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Vol. 7 No. 1 JANUARY, 1953

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LONDON
BRITISH MEDICAL ASSOCIATION
TAVISTOCK SQUARE, W.C.1

YEARLY SUBSCRIPTION (4 NUMBERS) £2 2s. 0d. U.S.A. $7.00 SINGLE NUMBER 12s. 6d.

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Engle, E. T., and Shelesnyak, M. C. (1934). *Hum. Biol.*, **6**, 431.
Fluhmann, C. F. (1936). *Amer. J. Obstet. Gynec.*, **31**, 573.
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Medical
Soth.

Brit. J. prev. soc. Med. (1953), 7, 1–8

DIFFERENTIAL FERTILITY BETWEEN WOMEN OF BLOOD GROUPS O AND A*

BY

R. L. KIRK, M. KIRK, and N. S. STENHOUSE

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Introduction

The discovery of the Rh blood groups by Landsteiner and Wiener (1940), and the subsequent demonstration by Levine and others (1941) of their role in the aetiology of haemolytic disease of the newborn, has re-opened the problem of incompatibility between mother and foetus with respect to the A-B-O blood group antigens. Levine (1943) reviewed a number of family studies of the inheritance of blood groups and reached the conclusion that there was a significant deficiency of offspring in matings between mothers of blood group O and fathers of group A, compared with those where the mother was of group A and the father of group O.

More recently Waterhouse and Hogben (1947) have made a detailed analysis of twelve published studies in which the A-B-O blood groups of parents and children have been listed. Their samples were carefully selected on the basis of reliability of technique and randomness of the population investigated. A significant deficiency of children was found in the mating group O-mother : A-father compared with the reciprocal group, this deficiency being due entirely to the selective loss of A children of the group O mothers. The effect was more marked at higher birth ranks. They concluded that provisional estimates suggest that A-B-O *iso*-immunization is responsible for the loss of about 25 per cent. of the A children expected from marriages between group O mothers and A fathers, or a loss of roughly 3 per cent. of all conceptions.

Race and Sanger (1950) point out the difficulty of reconciling a loss of this magnitude with the constancy of the frequencies for the A-B- and R genes over long periods of time, unless some compensatory mechanism is at work. At least two points require further study before our ideas on the possible nature of such compensatory mechanism can be clarified. These are:

(*a*) the provision of evidence of a collateral nature to substantiate the magnitude of the iso-immunization effect with respect to the agglutinogen A reported by Waterhouse and Hogben (1947),

(*b*) a more detailed investigation of the relative fertility of group O women and group A women in a socially homogeneous population.

The present paper records the results of an analysis of the blood-type and previous pregnancy experience of women giving birth to children in a large maternity hospital during the years 1948 to 1951. An effect of the magnitude of that reported by Waterhouse and Hogben for family studies should manifest itself in such a sample by a changing distribution of women of blood groups O and A with age and parity.

Since this work was started, Boorman (1950) and Bryce and others (1950) have published papers relating to blood group distributions in a series of mothers and infants, the data having been obtained from maternity hospitals in England and Australia. Bryce and others find a significant excess of group AB among the mothers compared with their children, both for their Australian sample only, and for the Australian sample combined with Boorman's English sample. They suggest that some A and B genes may be replaced by especially fertile AB mothers. Where the data of these workers has been presented in sufficient detail comparisons will be made with results obtained in the present investigation.

Methods of Collecting Data

The data used in the present analysis was collected from the record cards of admissions to the King Edward Memorial Hospital, Perth. Selection was made for clinic patients; persons referred to the hospital by private doctors were rejected. In this way a comparatively socially-homogeneous group unselected for complications of pregnancy was made available for analysis. Details of previous pregnancy experience, together with information relating to age, outcome of present pregnancy, etc., is routinely listed on the cards.

The information relating to previous pregnancy experience, particularly miscarriages and to a lesser extent stillbirths, is likely to be misrepresented by the women concerned. We have assumed that the

* This investigation was aided by a grant from the Australian National Health and Medical Research Council.

inaccuracies are distributed proportionately between the different groups. A-B-O and Rh blood group determinations are carried out on all clinic patients by workers in the Public Health Department Blood Group Laboratory attached to the hospital. A uniformity of testing technique is assured, and some of the patients are retested at monthly intervals during pregnancy.

The sample studied is a biased selection of women of the same age groups in the population in so far as all must be experiencing pregnancy when the records are entered. Those that miscarry after they have first attended the clinic, and who report their miscarriage, are appropriately listed.

Analysis of Data

During the 4-year period under review the sample was changing slightly in blood group distribution and in age composition. Table I*A* gives the A-B-O blood group distribution for 6,121 mothers, Table I*B* records the corresponding Rh frequency (anti-*D*).

Fig. 1.—Difference in average number of pregnancies per woman, A–O

Table I*A*

A-B-O BLOOD-GROUP DISTRIBUTION BY YEAR
(Total Perth Sample)

Year			1948	1949	1950	1951	All Years
Group	O	Number	437	621	816	871	2745
		Per cent.	46·0	43·5	45·2	45·0	44·8
	A	Number	407	619	756	778	2560
		Per cent.	42·9	43·3	41·8	40·2	41·8
	B	Number	84	151	178	216	629
		Per cent.	8·8	10·6	9·9	11·2	10·3
	AB	Number	21	38	57	71	187
		Per cent.	2·2	2·6	3·2	3·7	3·1
All Groups		Number	949	1429	1807	1936	6121
		Per cent.	99·9	100·0	100·1	100·1	100·0

$\chi^2 = 12{\cdot}399$ $\quad 0{\cdot}10 < p < 0{\cdot}20$

Table I*B*

Rh BLOOD-GROUP DISTRIBUTION BY YEAR
(Total Perth Sample)

Year			1948	1949	1950	1951	All Years
Group	Rh+	Number	816	1,185	1,502	1,618	5,121
		Per cent.	86·0	82·9	83·1	83·6	83·7
	Rh−	Number	133	244	305	318	1,000
		Per cent.	14·0	17·1	16·9	16·4	16·3
Total		Number	949	1,429	1,807	1,936	6,121
		Per cent.	100·0	100·0	100·0	100·0	100·0

$\chi^2 = 4{\cdot}696$ $\quad 0{\cdot}10 < p < 0{\cdot}20$

The frequency of Group B and AB have tended to increase, and although the analysis of the complete table does not indicate a significant deviation from expectation, a comparison of the combined group O-A with the combined group B and AB frequencies suggests that this trend is a real one ($\chi^2 = 8{\cdot}137$, $0{\cdot}02 < P < 0{\cdot}05$). It is also clear that the change in the age composition of the 4-year samples in Table II, with a proportionate decrease in the under-20 age group and an increase in the 26–30 age group is also significant ($\chi^2 = 30{\cdot}954$, $0{\cdot}001 < P < 0{\cdot}01$).

Table II

AGE-GROUP DISTRIBUTION BY YEAR
(Total Perth Sample)

Year			1948	1949	1950	1951	All Years
Age Group	20 and under	Number	213	299	351	354	1,217
		Per cent.	22·4	20·9	19·4	18·3	19·9
	21–25	Number	349	501	653	692	2,195
		Per cent.	36·8	35·1	36·9	35·7	35·9
	26–30	Number	183	322	431	503	1,439
		Per cent.	19·3	22·6	23·8	26·0	23·5
	31–35	Number	113	176	221	211	721
		Per cent.	11·9	12·3	12·2	10·9	11·8
	36–40	Number	69	112	116	151	448
		Per cent.	7·3	7·8	6·4	7·8	7·3
	Over 40	Number	22	19	35	25	101
		Per cent.	2·3	1·3	1·9	1·3	1·7
	All Ages	Number	949	1,429	1,807	1,936	6,121
		Per cent.	100·0	100·0	99·9	100·0	100·1

$\chi^2 = 30{\cdot}954$ $\quad 0{\cdot}001 < p < 0{\cdot}01$

The change in the frequency of group B and AB suggested that recent arrivals in Australia from countries with relatively higher frequencies of group B than for typical English and Australian populations were making a significant contribution to this effect. Accordingly, we have differentiated the sample on the basis of name (*cf.* Hart, 1944; Roberts, 1948) into two groups:

(*a*) of English name, and
(*b*) of non-English name.

The second group comprises people drawn from Eastern, Central, and Southern Europe in the majority with a fairly substantial number of Dutch migrants. The country of origin of these people all have frequencies for the B-gene higher than that in Great Britain. (Wiener, 1943.)

The tendency for the frequency of B and AB to increase in recent years in the total sample disappears if women of English name only are included. The frequency for A-O combinations against B-AB in this group (Table III*A*) shows no heterogeneity ($\chi^2 = 3{\cdot}751, 0{\cdot}30 > P > 0{\cdot}20$). Further, the heterogeneity of the sample with regard to age groups is considerably reduced if women of non-English name are removed, although there is still a slight

TABLE III*A*

BLOOD-GROUP DISTRIBUTION OF WOMEN OF ENGLISH NAME BY YEAR

Year			1948	1949	1950	1951	All Years
Group	O	Number	388	558	665	716	2,327
		Per cent.	47·0	43·9	45·7	47·0	45·8
	A	Number	351	559	609	607	2,126
		Per cent.	42·5	44·0	41·8	39·8	41·9
	B	Number	72	123	143	156	494
		Per cent.	8·7	9·7	9·8	10·2	9·7
	AB	Number	15	31	39	46	131
		Per cent.	1·8	2·4	2·7	3·0	2·6
All Groups		Number	826	1,271	1,456	1,525	5,078
		Per cent.	100·0	100·0	100·0	100·0	100·0

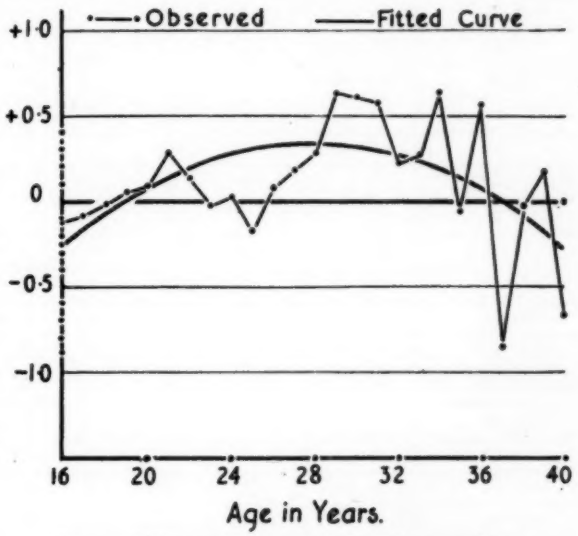
TABLE III*B*

AGE-GROUP DISTRIBUTION OF WOMEN OF ENGLISH NAME BY YEAR

Year			1948	1949	1950	1951	All Years
Age Group	20 and under	Number	190	275	296	314	1,075
		Per cent.	23·0	21·6	20·3	20·6	21·2
	21–25	Number	300	435	525	545	1,805
		Per cent.	36·3	34·2	36·1	35·7	35·5
	26–30	Number	162	291	329	370	1,152
		Per cent.	19·6	22·9	22·6	24·3	22·7
	31–35	Number	95	157	183	160	595
		Per cent.	11·5	12·4	12·6	10·5	11·7
	36–40	Number	60	98	91	116	365
		Per cent.	7·3	7·7	6·2	7·6	7·2
	Over 40	Number	19	15	32	20	86
		Per cent.	2·3	1·2	2·2	1·3	1·7
	All Ages	Number	826	1,271	1,456	1,525	5,078
		Per cent.	100·0	100·0	100·0	100·0	100·0

tendency for the 1950 and 1951 sample of women of English name to contain a relatively higher proportion of women aged 21–30 than in the previous 2 years (Table III*B*). It seems reasonable to assume, therefore, that the women of English name are a socially homogeneous population with respect to their A-B-O blood group distributions, and at present there is no reason to suppose that socio-economic conditions will affect the child-bearing capacity of women in one blood group compared with those in another.

If, however, the figures for the average number of pregnancies experienced per woman in group O are compared with those for women in group A an interesting difference between the two groups emerges. Tables IV*A* and IV*B* (overleaf) record the pregnancy rank of Rh-positive women of English name in blood groups O and A. Although the overall pregnancy experience of women in the two groups is almost identical (being slightly, but not significantly, higher for women of group A), there is a marked deficiency of pregnancies experienced by women of group O between 25 and 35, with a tendency toward a marked excess of pregnancies in the same group for women above the age of 35. Orthogonal polynomials were fitted to this series of differences in average number of pregnancies between women in group O and A for each year of age from 16 to 40 (see Figure). The result shows that the observed trend is highly significant, the bulk of the variance being attributed to the binomial expression.



FIGURE—Difference in average number of pregnancies per woman, A—O

The same trend is observable in the extremely heterogeneous group of women of non-English name (Table V). A polynomial analysis by each year of age of the Rh-positive women in the total sample again yields a highly significant result.

TABLE V

AVERAGE NUMBER OF PREGNANCIES IN Rh-POSITIVE WOMEN

Women		Of Non-English Name (694)		All in Perth Sample (4,444)	
Blood Group ..		O (343)	A (351)	O (2,273)	A (2,171)
Age Group	20 and under	1·3191	1·3617	1·3451	1·3750
	21–25	2·0887	1·9781	2·0961	2·1475
	26–30	2·5200	2·6526	3·0055	3·3460
	31–35	3·1351	3·2857	3·8706	4·1374
	36–40	4·1000	4·1200	5·1864	5·1074
	Over 40	5·4000	5·0000	6·5909	6·3448
All Ages		2·4461	2·4302	2·6912	2·7835

TABLE IV*A*

NUMBER OF PREGNANCIES EXPERIENCED BY Rh-POSITIVE GROUP O WOMEN OF ENGLISH NAME

Age	Number of Pregnancies											Total Women	Total Pregnancies	Average Pregnancies per Woman
	1	2	3	4	5	6	7	8	9	10	10+			
Total (16 and under)	18	—	1									19	21	1·1053
17	30	6										36	42	1·1667
18	69	13	2									84	101	1·2024
19	85	32	5	2								124	172	1·3871
20	88	43	9	1	1							142	210	1·4789
Total (20 and under)	290	94	17	3	1							405	546	1·3481
21	81	50	16	2	—	—	1					150	244	1·6267
22	57	61	25	5	2	1	—					151	290	1·9205
23	33	54	31	11	1	—	—					130	283	2·1769
24	24	51	35	11	4	1	—					126	301	2·3889
25	20	46	33	16	3	2	—					120	302	2·5167
Total (21–25) ..	215	262	140	45	10	4	1					677	1,420	2·0975
26	15	34	41	12	6	3	2					113	316	2·7965
27	13	39	26	21	11	—	3					113	329	2·9115
28	12	16	28	15	10	5	1					87	275	3·1609
29	8	14	19	18	8	4	2	2				75	259	3·4533
30	8	12	8	9	10	4	3	1	1			56	204	3·6429
Total (26–30) ..	56	115	122	75	45	16	11	3	1			444	1,383	3·1149
31	5	5	9	9	12	2	1	—	—			43	157	3·6512
32	4	14	9	11	5	4	4	—	1			52	189	3·6346
33	3	5	17	10	5	4	3	3	1			51	207	4·0588
34	1	6	8	7	8	3	2	1	1			37	154	4·1622
35	2	4	4	7	7	3	3	5	—			35	164	4·6857
Total (31–35) ..	15	34	47	44	37	16	13	9	3			218	871	3·9954
36	2	4	11	10	4	7	5	—	4			47	216	4·5957
37	—	1	1	3	6	6	1	2	2	—	1	23	136	5·9130
38	1	3	3	7	2	3	2	3	1	3	—	28	149	5·3214
39	—	2	4	4	2	3	1	3	2	2	2	25	152	6·0800
40	—	2	4	1	6	1	3	3	1	2	1	24	142	5·9167
Total (36–40) ..	3	12	23	25	20	20	12	11	10	7	4	147	795	5·4082
Total (Over 40)	1	—	3	6	8	4	2	3	3	6	3	39	263	6·7436
Grand Total ..	580	517	352	198	121	60	39	26	17	13	7	1,930	5,278	2·7347

It would be expected that, if women of a particular age group are experiencing fewer pregnancies if they belong to group O than if they belong to group A, they will be underrepresented in a maternity hospital sample for those ages compared with a sample of all women. In the present series this is clearly the case. Table VI*A* (overleaf) records the ratio of O : A Rh-positive women in 5-year age groups. Table VI*B* (overleaf), based on Boorman (1950), reveals the same trend in this smaller sample. A polynomial analysis by each year of age from 16–40 for women of English name in our own series indicates that the trend is significant. Under the age of 25, group O women appear in the sample in the same proportion as they do in the total sample. Between 25 and 35, group O is considerably underrepresented, and over 35 an increase in the proportion of group O takes place which compensates for the deficiency in the preceding 10-year period. Both in our own series and in Boorman's a notable feature is the

TABLE IV*B*

NUMBER OF PREGNANCIES EXPERIENCED BY Rh-POSITIVE GROUP A WOMEN OF ENGLISH NAME

Age	Number of Pregnancies											Total Women	Total Pregnancies	Average Pregnancies per Woman
	1	2	3	4	5	6	7	8	9	10	10+			
Total (16 and under)	11											11	11	1·0000
17	36	3										39	42	1·0769
18	66	13	1									80	95	1·1875
19	72	44	4									120	172	1·4333
20	73	50	11	1								135	210	1·5556
Total (20 and under)	258	110	16	1								385	530	1·3766
21	51	54	26	4	—	1						136	259	1·9044
22	40	56	31	7	1	—						135	278	2·0593
23	35	54	28	12	—	1						130	281	2·1615
24	24	30	42	13	1	—	1	1				112	282	2·5179
25	25	54	27	12	3	2	—	—				123	289	2·3496
Total (21–25) ..	175	248	154	48	5	4	1	1				636	1,389	2·1840
26	10	28	26	18	7	2	—	—				91	263	2·8901
27	9	29	29	25	7	2	2	1				104	323	3·1058
28	11	20	20	12	12	5	2	3	—	1		86	297	3·4535
29	5	11	13	17	12	12	3	—	1	1		75	306	4·0800
30	1	13	14	15	16	10	4	—	1	—	1	75	319	4·2533
Total (26–30) ..	36	101	102	87	54	31	11	4	2	2	1	431	1,508	3·4988
31	4	5	13	10	11	6	4	2	1	—	—	56	237	4·2321
32	3	11	13	14	3	4	5	1	—	1	—	55	212	3·8545
33	2	7	8	10	7	4	6	1	—	1	—	46	199	4·3261
34	2	3	6	7	3	3	2	—	2	3	—	31	149	4·8065
35	5	—	5	5	7	4	3	1	—	1	1	32	149	4·6563
Total (31–35) ..	16	26	45	46	31	21	20	5	3	6	1	220	946	4·3000
36	—	4	7	4	5	5	1	2	3	2		33	170	5·1515
37	—	5	4	5	2	7	4	—	2	—	1	30	153	5·1000
38	—	—	4	6	7	2	3	2	2	—	—	26	138	5·3077
39	—	1	1	1	1	2	3	5	—	—	—	14	87	6·2143
40	—	2	4	4	3	2	1	3	1	—	1	21	110	5·2381
Total (36–40) ..	—	12	20	20	18	18	12	12	8	2	2	124	658	5·3065
Total (Over 40)	—	1	1	2	5	3	3	3	3	2	1	24	159	6·6250
Grand Total ..	485	498	338	204	113	77	47	25	16	12	5	1,820	5,190	2·8516

high ratio of O/A women for the group over 40 years of age.

A further indication of the difference in pregnancy experience in the two groups of women is to be found in the distribution of group O and A among women experiencing their first pregnancy compared with those who have experienced at least two. Both for the women of English name and for the total Perth sample there is a significant excess of group O women experiencing their first pregnancy. Table VII*A* (overleaf) gives $\chi^2 = 5{\cdot}336$ $(0{\cdot}02 < P < 0{\cdot}05)$ and $\chi^2 = 4{\cdot}795$ $(0{\cdot}02 < P < 0{\cdot}05)$ respectively.

The same discrepancy is observable in Boorman's sample, more than the total excess of group O women being found among the primiparae (Table VII*B*, overleaf). The difference for Boorman's sample, however, is not significant. This may be due solely to sample size, but the relatively smaller number of multiparous women in the English study

TABLE VI*A*

NUMBER OF Rh-POSITIVE WOMEN OF GROUP O AND GROUP A

Women		Of English Name			Total in Perth Sample		
Blood Group		O	A	O/A	O	A	O/A
Age Group	20 and under	405	385	1·052	452	432	1·046
	21–25	677	636	1·064	801	773	1·036
	26–30	444	431	1·030	544	526	1·034
	31–35	218	220	0·991	255	262	0·973
	36–40	147	124	1·185	177	149	1·188
	Over 40	39	24	1·625	44	29	1·517
Total All Ages		1,930	1,820	1·060	2,273	2,171	1·047

TABLE VI*B*

NUMBER OF WOMEN IN BOORMAN'S SAMPLE

Blood Group		O	A	O/A
Age Group	14–19	40	35	1·143
	20–29	487	490	0·994
	30–34	185	187	0·989
	35–39	107	114	0·939
	40–49	53	30	1·767
	Not Known	20	16	1·250
All Ages		892	872	1·023

TABLE VII*A*

NUMBER OF Rh-POSITIVE GROUP O AND A WOMEN EXPERIENCING THEIR FIRST PREGNANCY COMPARED WITH WOMEN EXPERIENCING SECOND PREGNANCY OR HIGHER

Women		Of English Name				In Total Perth Sample			
Pregnancy		First		Second or Higher		First		Second or Higher	
Blood Group		O	A	O	A	O	A	O	A
Age Group	20 and under	290	258	115	127	324	291	128	141
	21–25	215	175	462	461	260	228	541	545
	26–30	56	36	388	395	80	58	464	468
	31–35	15	16	203	204	24	18	231	244
	36–40	3	—	144	124	6	4	171	145
	Over 40	1	—	38	24	1	—	43	29
All Ages		580	485	1,350	1,335	695	599	1,578	1,572

TABLE VII*B*

BASED ON BOORMAN (1950)

Women	Primiparae		Multiparae	
Blood Group	O	A	O	A
All Ages	514	482	378	390

is undoubtedly of importance in masking any effect of birth rank.

MISCARRIAGES AND STILLBIRTHS

The information relating to the number of miscarriages and stillbirths is unreliable as far as previous pregnancies are concerned. Women are asked to record any miscarriages and stillbirths experienced previously when first attending the prenatal clinic: confusion over the nature of miscarriages and stillbirths is not uncommon, and miscarriages in particular are likely to be understated in some cases, and overstated in others. The available information for Rh-positive women of English name of the groups O and A in our sample is presented in Table VIII. The overall miscarriage and stillbirth frequency is identical for groups O and A women, and no significant difference by age can be demonstrated. If miscarriages and stillbirths are removed from the sample the number of live births

TABLE VIII

TOTAL NUMBER OF STATED MISCARRIAGES AND STILLBIRTHS EXPERIENCED BY WOMEN Rh-POSITIVE OF ENGLISH NAME

Experience		Miscarriage		Stillbirth		Miscarriage + Stillbirth	
Blood Group		O	A	O	A	O	A
Age Group	20 and under	21	14	10	10	31	24
	21–25	71	72	23	29	94	101
	26–30	88	102	22	26	110	128
	31–35	48	48	26	27	74	75
	36–40	44	22	16	15	60	37
	Over 40	13	9	10	5	23	14
All Ages		285	267	107	112	392	379

per woman in groups O and A follows the same distribution as that previously described for total pregnancies.

DISCUSSION

The selective loss of A children to group O mothers in the mating group O-mother : A-father demonstrated by Waterhouse and Hogben (1947), should result in an apparent reduction of the average number of pregnancies with increasing age in all group O women unless some form of compensation occurs. The present analysis of total pregnancy experience for Rh-positive women of groups O and A in a socially homogeneous maternity hospital sample suggests that at least one such compensatory mechanism may be operative.

The observed series for the difference in the average number of pregnancies with age between women of group O and group A could result from the operation of several factors:

(*a*) Group O women in compatible mating groups have an innately higher fertility than group A women.

(*b*) Group O women in incompatible mating groups prolong their attempts to have children, and meet with greater success above the age of 35.

(*c*) Group A women also suffer from a reduction in fertility, starting at a later age than in women of group O but becoming relatively more severe by the age of 40.

These three alternatives are all capable of explaining the phenomenon. At the present time the evidence favours the hypothesis that group O women in compatible mating groups have an innately higher fertility than women of group A. In the study of Waterhouse and Hogben the average number of children in families where the mother is group O (3·38) is identical with that for families where the mother is group A (3·37). But it is much higher in O × O families (3·46) than in A × A families (3·17). The investigation of Boorman (1950) lends further indirect support to the view that group O women are innately more fertile than group A women unless married to a group A husband. Women under 20 years of age who are classed as incompatible for A-B-O groupings, *i.e.* mainly group O women, on the basis of the blood group of their last child have experienced slightly more pregnancies than women classed as compatible (1·43 as against 1·05). But the incompatible group, where the incompatible antigen is group A, suffer a marked deficiency in child-bearing above the age of 20 compared with the compatible group, the difference increasing steadily. At age of 40–49 the respective figures are 2·91 and 3·86. Finally, in the present series, group O mothers experience a higher number of pregnancies under age 19 than do group A mothers. This excess occurs before the effects of incompatibility have become apparent and probably represents a real excess on the part of group O women.

If this excess fertility of group O women in compatible matings is accepted, the following sequence of events would satisfy the observed facts.

Mothers of group O and group A occur in the total sample in the same proportions as do such women in the general population (Bryce and others, 1950).

Group O mothers show a slight initial excess in number of pregnancies experienced.

Some group O mothers belong to incompatible mating groups, the largest of these being incompatible for the A antigen (44 per cent. of all O mothers). These women have a progressive reduction in relative fertility compared with group A women, so that, not only are there proportionately fewer women of group O in the sample between ages 25 and 35, but each of them experiences fewer pregnancies on the average. One hundred group O Rh-positive women aged 26–35 have on the average 36 children fewer than 100 group A Rh-positive women of the same age. The discrepancy would be more marked probably if incompatible group O women only were included.

Above the age of 35 women of group A tend to complete their families more quickly than the group O women in the compatible class, who continue to bear children past the age of 40 more frequently than do women of group A. In the Perth sample studied here 100 group O Rh-positive women above the age of 35 have on the average sixteen more children than 100 group A Rh-positive women of the same age.

This excess fertility of group O women in compatible mating groups could explain the replacement of O-genes lost through the selective elimination of heterozygous children in the mating group O-mother : A-father. It could not explain, however, the relacement of an equal number of A-genes lost at the same time. Further studies with larger samples to enable the accurate assessment of the contribution in other mating groups involving phenotypes B and AB may reveal the source of this replacement through the operation of a similar compensatory mechanism involving B and AB matings with women of group A. The excess of AB mothers noted by Bryce and others (1950) may play a part in this replacement.

Summary

(1) Data are presented on the A-B-O and Rh blood groups, age, and pregnancy experience of women admitted to a large maternity hospital in Australia during the years 1948–51.

(2) A detailed analysis of the material relating to Rh-positive women of English name is given.

(3) Women of blood groups O and A exhibit a differential pregnancy experience with age. In the earliest age groups, group O women have had slightly more children than group A women. Between 25 and 35 years of age, however, group O women experience fewer pregnancies than those of group A, the position becoming reversed above the age 35. Orthogonal polynomials have been fitted to the differences in average number of pregnancies between women of groups O and A for each year of age from 16–40. The result shows the trend to be highly significant.

(4) The number of group O women in the sample follows the same trend, there being proportionately fewer women of group O between 25 and 35, and an excess above age 35, which is most marked above age 40.

(5) There is a significant excess of group O women who are experiencing their first pregnancy.

(6) A hypothesis is advanced which suggests that women of group O in a compatible mating group are on the average more fertile than either women of group O in an incompatible mating group or women of group A.

We are indebted to Matron Walsh and the staff of the King Edward Maternity Hospital, Perth, for granting facilities to collect the data presented here. We are also indebted to Dr. W. A. Young of the West Australian Department of Public Health, and to Drs. G. A. Kelsall and J. Watson for their encouragement and help.

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Brit. J. prev. soc. Med. (1953) **7**, 9–13

EPILEPSY IN SCHOOL CHILDREN

BY

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In a previous communication it was suggested that about 0·3 per 1,000 children should be in special schools for epileptics (Henderson, 1948). Since, however, many factors have to be considered before a child is recommended for a boarding special school, it was decided to examine all the children in certain representative areas who were known by the School Medical Officers to be epileptic *and educable*, in order to find out how many were in need of treatment and education in special schools and what effects epilepsy had on children living in the community.

The investigation was made in Carlisle, Bolton, York, Derby, Cambridge, Ipswich, Norwich, Bedford, Luton, Norfolk, East and West Suffolk, Cambridgeshire, Isle of Ely, Huntingdonshire, Bedfordshire and part of the Metropolitan area (about one-third of Middlesex and West Ham). These areas had a school population of 355,000, being about 6 per cent. of the school population of England and Wales. Time did not permit a wider enquiry.

Children were seen in their own homes, at school clinics, or in their schools. At least one parent was always interviewed. The school medical and educational records of every child were examined, and were discussed with the school doctors and, often, with the teachers. Each child was given an intelligence test (Revised Terman-Merril—Forms L or M) and a detailed history was recorded from the parents.

Incidence

Altogether 430 educable children (1·2 per 1,000) were found to be epileptic (Table I). The incidence was 1·1 per 1,000 in the metropolitan and rural areas and 1·5 per 1,000 in the towns.

Of the 430 children, 316 had major, 65 had minor, and 49 had both types of seizures; 250 were boys and 180 were girls. Of these children 365 were examined; 49 of the remaining 65 were in boarding special schools for epileptic children and the other sixteen were not seen either because they were ill or because their parents refused to allow them to be examined. Only about half a dozen parents were unwilling to take part in this investigation.

TABLE I

INCIDENCE OF EPILEPSY IN SCHOOL CHILDREN

Area	School Population	Epileptic Children	
		Number	Incidence per 1,000
Northern towns	64,000	94	1·5
Towns in East Anglia and in some Home Counties ..	58,000	85	1·5
Metropolitan area (Parts of Middlesex and West Ham)	110,000	118	1·1
Rural areas (East Anglia and some Home Counties) ..	123,000	133	1·1
Totals	355,000	430	1·2

Frequency of Seizures

The frequency of fits among the 365 children examined was as follows:

daily, 26 (six with grand mal);
weekly, 32 (24 with grand mal);
monthly, 39 (29 with grand mal);
less frequently than once a month, 268 (of whom 193 had fits at intervals of more than 6 months).

A total of 29 children (ten with grand mal) had fits on the day of examination, and 46 (33 with grand mal) had had them in the previous week. But on the other hand, 139 (38 per cent.) had not had a fit for more than one year, and fifty (14 per cent.) had been free from fits for more than 3 years. Only 34 (9 per cent.) of the 365 children gave a history of fits in school.

It was difficult to assess the severity of the seizures from the descriptions given by parents; the period of unconsciousness was frequently confused with the deep sleep that often followed a major attack. But it was evident that a number of the children, including some who had few or infrequent fits, had experienced very severe seizures. Eight had been sent to hospital in status epilepticus; six of these had been fit-free for at least one year before the visit, and the other two were still having attacks at least once a week.

Intelligence

Of the 365 children, 59 per cent. were of average intelligence, 31 per cent. were below, and only

10 per cent. were above the average at the time of the examination (see Table II).

TABLE II

INTELLIGENCE OF CHILDREN EXAMINED

I.Q.	Number	Per cent.
Less than 70	54	15
70–84	60	16
85–114	215	59
115+	36	10
Total ..	365	100

Severe and frequent fits and the taking of drugs for several years are almost bound to have some effect on the personality of an epileptic child; unless one can observe such a child from the onset of the seizures, and over a long period, it is impossible to assess the full effect of these influences.

It was found that 188 (66 per cent.) of those with major, and 63 (78 per cent.) of those with minor epilepsy had an I.Q. of 85 or more (Table III). Of the 97 children who had fits at least once a month 41 (42 per cent.) had an I.Q. below 85, compared with 73 (27 per cent.) of 268 children with an I.Q. below 85 who had seizures at longer than monthly intervals.

The medical superintendents of the special schools attended by the 49 children who were not seen, kindly gave the results of intelligence tests performed in the schools: 28 (57 per cent.) had an I.Q. of less than 85, and only three (6 per cent.) one of 85 or more. If these 49 children had been added to the 365 examined, the number with an I.Q. below 85 would then have been increased from 114 (31 per cent.) to 142 (34 per cent.). It has to be remembered that no account was taken of children also known to be ineducable in the sample population; but the general opinion is that less than 1 per cent. of the child population falls into this category.

All that can reasonably be said about this small sample population is that the percentage of epileptic children below average intelligence was rather higher in the groups with frequent and major seizures; and that, compared with the normal school population, there were rather more children below and fewer above, average intelligence. It would, however, be very misleading to form an opinion of the intelligence of epileptic children from experience of children in special schools.

BEHAVIOUR

Of the 365 children examined, 44 (12 per cent.) were described as emotionally disturbed or badly behaved. These 44 children may be classified as follows:

28 were boys and 16 were girls.

37 had major and 7 minor epilepsy.

Six had daily seizures; twelve had seizures at least once a week, six at least once a month; three about once every 3 months, two about once every 6 months, and the other fifteen infrequently.

Nineteen had an I.Q. below 70.

Thirty were in ordinary schools; five were in special schools for educationally sub-normal children; and nine had been excluded from school.

Seven were attending child guidance clinics; two had been in mental hospitals.

The following selection of case notes illustrates the various behaviour and emotional difficulties exhibited:

GIRL, AGED 13 YEARS (I.Q. 54).—Used to have severe major attacks but last had one 9 months before examination; on phenobarbitone and epanutin. Would be well behaved and good-natured for weeks and would then suddenly become bad-tempered and quarrelsome and kick and scream at anyone who remonstrated with her; almost certainly ineducable and unemployable.

GIRL, AGED 7 YEARS (I.Q. 67).—Major attacks weekly. On phenobarbitone. Restless; violent with other children; destructive; created pandemonium in school and had to be excluded.

BOY, AGED 6 YEARS (I.Q. 111).—Daily attacks of petit mal. No treatment. Was obstinate and very disobedient and

TABLE III

INTELLIGENCE IN RELATION TO TYPE AND FREQUENCY OF FITS

Frequency of Fits	I.Q.				Total Children	
	Major		Minor			
	85 or Above	Below 85	85 or Above	Below 85	Number	Per cent.
At least once a week	14	16	21	7	58	16
" " once in 1–4 weeks ..	16	13	5	5	39	11
" " once in 1–3 months ..	21	9	5	1	36	10
" " once in 4–6 months ..	20	14	3	2	39	11
Longer than 6 months	117	43	29	4	193	52
Totals	188 (66 per cent.)	95 (34 per cent.)	63 (78 per cent.)	19 (22 per cent.)	365	100

came home late at night. Mother was happy-go-lucky and had no control over him, or over an elder non-epileptic brother who was just as badly behaved.

BOY, AGED 10 YEARS (I.Q. 83).—A major attack about once a month. No treatment. Was obstinate and disobedient. In school he cheeked his teacher and from time to time during prayers muttered audibly, "old skinflint, old skinflint", to the teacher's annoyance and his classmates' delight. He sat at the back of the class and ignored the teacher except when he set out to goad her.

BOY, AGED 8 YEARS (I.Q. 114).—Daily attacks of petit mal. On phenobarbitone. He was spoilt by his mother during his father's absence abroad for 4 years, and on his father's return became jealous of him and once told him to go away and get killed. Very disobedient at home and had violent fits of temper when he threw things at his mother. He gave no trouble at school.

Since about 60 per cent. of the emotionally-disturbed children were below average intelligence (almost half being feeble-minded), it is impossible to say how much of the bad behaviour was due to innate poor intelligence, to epilepsy, or to a combination of both. Some of the parents were, themselves, emotionally unstable. It is noteworthy that only eight of the seventeen children with average, or higher, intelligence had parents who appeared to be emotionally mature.

If this sample population was representative, the bulk of epileptic children outside institutions are no more difficult than normal children; those who are emotionally disturbed are, however, exceedingly troublesome.

MEDICAL TREATMENT

That most parents become seriously concerned when their children develop epilepsy is emphasized by the fact that 236 (65 per cent.) of the 365 children had been to hospitals for investigation and advice: 24 were known to have had an electroencephalogram examination.

Treatment appeared to be inadequate in 36 cases, and a few children were having no treatment. The following cases are typical:

GIRL, AGED 11 YEARS.—Had had severe major attacks since the age of 5 years; they were occurring about once a fortnight, and she had had six in school. Her only treatment was ½ gr. phenobarbitone once nightly.

BOY, AGED 13 YEARS.—Had been having major attacks at about monthly intervals from the age of 3 years. He had had no treatment. According to his mother, one doctor told her to give the boy "Epsom salts", and another doctor told her not to worry as the lad would "grow out of it".

BOY, AGED 14 YEARS (I.Q. 107).—Had been having about three major attacks a fortnight, and they were becoming more frequent and more severe. He was on ¼ gr. luminal thrice daily which he fetched periodically from his doctor's surgery, but he had not seen the doctor for over a year.

Although the majority were having satisfactory treatment, it was distressing to find some who were not receiving the care they required. Sometimes the parents were at fault, at other times the doctor. Most of the patients had responded to treatment; 73 per cent. had fits less frequently than once a month, about half of these at intervals longer than 6 months, and about a quarter had none for over 2 years. On the other hand fifty children (14 per cent.) were becoming worse or showing no improvement: of these 33 were receiving no treatment or treatment that was unsatisfactory; 39 had grand and eleven petit mal.

Although a prognosis should always be cautious, that is no reason for giving the parents of an epileptic child no hope, as the following case histories show:

GIRL, AGED 14 YEARS (I.Q. 105).—Began to have attacks of petit mal at the age of 3 years; and had at least twenty to thirty a day. She was taken to a well-known London hospital and saw one of the senior physicians, who, according to the mother, pronounced that the child was "incurable" and would deteriorate. Though shaken, the mother was unconvinced; she went to another hospital, and here received the sensible advice that it was not possible to prophesy, then and there, how the child would progress; but, that if the parents persevered with the prescribed treatment, and handled the child with understanding, realizing her need for kindly discipline, there was a reasonable chance that the fits would be controlled. Eventually, the girl was sent to a special school for epileptics where she remained three years. When seen she was a pleasant, well-developed girl, and had been free from fits for more than a year.

BOY, AGED 9 YEARS (I.Q. 128).—Developed major and minor fits at the age of 5 years; at the beginning he had more than one hundred minor seizures a day and often injured himself when in a major fit. His parents were given a gloomy prognosis, but he attended a special school for 2 years. When seen he had been free from fits for 2 years and was doing well in an ordinary school. His home care was good.

If this sample population was representative, the prospect for a child with epilepsy is not so bleak as is often supposed.

FAMILY CARE

The high standard of parental care was impressive. All but a very small minority of the parents were

worried about the effect epilepsy might have on their children's prospects of employment and on their health and happiness when they left school. Some were over-anxious and others were emotionally unstable, but, according to their lights, they were doing their best for their children, although their efforts were often misdirected. Only nine of the 365 children appeared to have neglectful and careless parents: these families were well known to the school medical officers and teachers.

A difficult situation arose where a parent was so solicitous for his child's welfare that he (or more often she) had lost all sense of proportion, and by isolating the child from his fellows was undermining his will and placing his future in peril. The following cases are typical of this situation:

BOY, AGED 10 YEARS (I.Q. 120).—Had had major fits about once a fortnight from the age of 4 years. His mother was anxious and over-protective and would not permit him to take part in any game or physical exercise at school; immediately school was over he had to return home and was not allowed out unless accompanied by an adult. He was an only child and had no companions. He was intelligent and sensitive but miserably unhappy; his one desire was "to be sent away to school", and this oft-repeated wish had upset and hurt his mother.

BOY, AGED 13 YEARS (I.Q. 90).—Was having mild, major fits every few days, and at one time they had been severe. He had not been to school since the age of 5 years and was having treatment from a herbalist. His parents had refused to send him to a special school, and he spent his days in a back kitchen, was forbidden to do anything on his own, and never played with other children. He was in a pitiable state, illiterate, and very unstable emotionally.

In many ways, the lot of a child who was brought up in a dirty, feckless household, but was at liberty to associate with his fellows, was preferable to the life led by the two boys whose cases are described above.

EDUCATION

Of the 430 children known to be epileptic, and presumed to be educable, 317 were in ordinary primary or secondary modern schools, thirteen in grammar schools, 49 in special schools for epileptics, eighteen in schools for the educationally sub-normal, and six in schools for delicate children. The remaining 27 had been excluded from school, some for what appeared to be slight cause, and a few of these had received no education whatever. The following cases are typical:

GIRL, AGED 13 YEARS (I.Q. 95).—Had never been to school. She was having several major and minor fits a day. She was well-behaved and took a pride in her appearance but was illiterate.

GIRL, AGED 10 YEARS (I.Q. 114).—Used to have frequent major attacks and had last had one a month before examination. She had never had a fit in school; since most of them occurred at night, but she had been to school for a few days only in the past 3 years and was illiterate; the head teacher had discouraged her attendance lest she had a fit in school.

BOY, AGED 14 YEARS (I.Q. 94).—Had a major attack four months before examination; they used to be more frequent. He had been excluded from school 18 months previously and was spending his time cycling round the neighbourhood or attending the public swimming baths on his own.

Of the 365 children examined 35 appeared to be possible candidates for special schools for epileptics, although five of them might, on trial, have proved ineducable. If this estimate is correct and if this ratio is applied to the whole country it would seem, when allowance has been made for parental refusals, for children near school-leaving age, and for those who might be found to be ineducable, that accommodation in special schools (taking into account the children already there) is likely to be required for not more than 0·2 per 1,000 of the school population. In the earlier survey it was suggested that 0·3 per 1,000 children should have been in special schools for epileptics; but that survey was carried out by questionnaire and made no allowance for parental refusals, or for children who might have been found ineducable after trial. A rate of 0·3 per 1,000 would necessitate about 1,500 places in special schools, whereas if the rate was about 0·2 per 1,000 of the present school population of England and Wales only about 1,000 places would be required.

When the first survey was made in 1946 there was accommodation for 660 epileptic children in seven special schools. There are now over 800 epileptic children in eight special schools, and plans have been approved for another 200 places, including a small school for epileptic children with emotional or behaviour difficulties.

If the child population sampled in this second survey was representative of the whole, it may well be that the demand for special schools for epileptic children will be met within the next few years when the present building programme has been carried out. Modern drug treatment has undoubtedly controlled the seizures in many children who would formerly have been recommended for a special school.

It cannot be stated too often that the great majority of epileptic children should attend ordinary school.

Fitness for Employment

It would be unwise to be dogmatic on this subject but, on the available evidence, it was considered that at least 33 (9 per cent.) of the 365 children would almost certainly be unemployable. In 31 of these the main reason was poor intelligence: sixteen had an I.Q. below 55, fifteen between 55 and 60, and two between 61 and 70. Nine had fits at least once a week, another nine had them at least once a month, and eight had seizures at longer intervals than once in 6 months.

Although a few of the others might become unemployable if their fits remained uncontrolled, it appeared that the great majority would be able to earn their living.

Summary

(1) In a population of 355,000 school children from East Anglia, part of the metropolitan area, and certain home counties and northern towns, 430 epileptic children (1·2 per 1,000 school children) were identified.

(2) There were 250 boys and 180 girls; 316 had grand mal, 65 had petit mal, and 49 had both.

(3) Of the 430 children, 365 were examined and the following information was collected:

(*a*) *Frequency of Fits.*—73 per cent. had seizures less frequently than once a month: in 52 per cent. the interval between fits exceeded 6 months; 38 per cent. had been fit-free for at least one year, and 14 per cent. for more than 3 years. Only 9 per cent. had fits in school.

(*b*) *Intelligence.*—31 per cent.* (as compared with 25 per cent. of the general population) had an I.Q. below 85; 42 per cent. of those who had fits at least once a month had an I.Q. below 85 compared with 27 per cent. of those who had seizures at longer intervals. It is misleading to assess the intellectual capacity of epileptic children on experience gained in special schools where about 70 per cent. have an I.Q. below 85.

(*c*) *Behaviour.*—44 (12 per cent.) presented problems of behaviour; nineteen of these had an I.Q. below 70; some had very unstable parents. In short, the great majority of epileptic children outside institutions and special schools are no more difficult than normal children.

(*d*) *Medical Treatment.*—Although satisfactory in most cases treatment appeared to be inadequate in 36. 65 per cent. of the 365 children had attended hospital for investigation: 24 had had an electroencephalogram examination; fifty (14 per cent.) were either becoming worse or showed no improvement.

(*e*) *Family Care.*—In the great majority of families the children were given the greatest possible care. There were more over-anxious and over-protective parents than there were careless or indifferent ones.

(*f*) *Education.*—Of the 430 children known to be epileptic, 317 were in ordinary primary or secondary modern schools, thirteen in grammar schools, 49 in special schools for epileptics, 24 in other types of special school, and 27 had been excluded from school. When those already in special schools are included, it is estimated that 0·2 per 1,000 school children require treatment and education in special schools for epileptics.

(*g*) *Employability.*—33 (9 per cent.) would almost certainly be unemployable, mainly because of poor intelligence. A few others might become unemployable if their fits remained uncontrolled.

I acknowledge with gratitude the information and help given to me by the school medical officers of the areas chosen for the enquiry. They found the children for me and arranged my programme. That practically all the parents welcomed my visit was due to the influence of the school medical officers.

* If the children already in special schools for epileptics were included the percentage below 85 was 34.

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Brit. J. prev. soc. Med. (1953), **7**, 14–19

INCIDENCE OF DEATH FROM TUMOURS OF THE URINARY BLADDER

BY

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The investigation of possible environmental risks that may lead to an increase in the frequency of the occurrence of tumours of the urinary bladder requires a measure of the frequency with which the condition will be expected to occur in a sample of the population not regarded as being subjected to any known environmental hazard. For practical purposes, since no such population can be enumerated and defined, it is proposed to regard the total male population of England and Wales as representing such a sample.

If the frequency of the disease shows any marked tendency to age specificity, and if other influences at present not elucidated which vary at different dates produce a marked effect, then this measure must take into account both the age composition of the population under consideration, and the varying effect of contemporaneous conditions.

At present, English morbidity statistics have not reached a sufficiently high degree of excellence to allow a reliable estimate of this kind to be formed from them. However, the mortality statistics are of sufficient quality, and especially so in the case of bladder tumours, where all certificates showing mention of bladder tumour, classified into "cancer" or "tumours, benign and unspecified", have been collected separately at the General Register Office since 1921. This separation applies to males only, but since the immediate programme of investigation of risk is confined to predominantly male occupations, this limitation is at present immaterial. Moreover, this separation into certificates mentioning tumour of the bladder overcomes the technical difficulties introduced by the change of death certificate classification introduced in 1940 (Registrar General, 1949), if we adopt the convention of speaking of "death certification rate" instead of "death rate".

In fact, this "certification rate" will differ but slightly from the "death rate", since 97·5 per cent. of the death certificates are in fact assigned by the General Register Office to bladder tumour as the cause of death.

The other requirement for the estimation of an environmental risk is a detailed knowledge of the population at risk, both in regard to the dynamics of repletion, and the number of cases of the disorder discovered. In the present instance of bladder tumour, the hazards to be investigated are in the first case industrial, and many large industries do in fact possess records of dates of employment of men, possibly with the age at the time of employment. The type of estimation discussed here relies on the availability of this information, and is therefore largely applicable to possible hazards where the co-operation of the industry can be secured, or to the internal investigation of sections of the industry by the concerns themselves.

Theoretically, an estimate of the expected number of death certificates taking into account the factors enumerated could be made from an exhaustive analysis of the age-specific death certification rates for the appropriate years, and from the actual depletion by other causes of death of the population under consideration.

In practice, it is unlikely either that the complete death records of past works' populations can be obtained, or that the interested persons, frequently factory medical officers, will have access to the required demographical data or an inclination to obtain an estimate by such laborious means.

It is possible to make an approximation to the required estimate by using mean mortality data (life tables) for England and Wales, and by assuming certain relationships, discussed below, to be essentially of a linear nature throughout the three decades under consideration.

Another consequence of the separation of bladder tumour death certificates from other death certificates is that it has been possible to form an alphabetical index of such certificates for males in England and Wales. This index now covers the years

1936–50 and will be kept up-to-date. Should need arise the index can be extended to cover the period 1921–35 also. This index makes it possible for the Chester Beatty Research Institute to afford some help to works' medical officers or other interested persons in checking populations described by name and date of birth to find *prima facie* evidence of the possible number of bladder tumour death certificates that have actually occurred. In many cases further investigation will, of course, be necessary to obtain evidence of identity.

This observed frequency of death certificates can obviously only be expressed in whole numbers, and the relationship of these observed numbers to the expected frequency can be assumed to take the form of a Poisson distribution. Thus, for the observed number of death certificates, a limiting frequency for any given level of significance can be determined, and can be compared with the estimated frequency determined as described below.

The purpose of this communication is to give the mathematical and demographical background to the method discussed. For practical use in factories, tables have been constructed from the equations, and these tables, with instructions for their use, will form the subject of a separate communication (Case, 1953).

Given the numbers of the population involved, the date of starting work in the environment to be considered, and the age of the individual at starting, the equations allow of a complete solution, with fiducial limits, of the expected frequency without further recourse to demographical data. Withdrawals from the environment due to change of occupation or retirement do not affect the estimate required.

Methods and Materials

We had at our disposal the death certificates mentioning "cancer of the bladder" and "tumours of the bladder benign and unspecified" for the years 1921–50, for males, in England and Wales. Before all these data had become available, the certificates for 9 years, scattered throughout the 30-year period, had been used for a preliminary computation. This sample, when allowances for temporal differences had been made, differed so little from the total pooled data that the calculations based on it are used in much of the ensuing discussion. These data will be referred to as the "basal data" and indices calculated from them denoted by the suffix (*b*).

The certificates for each year were examined and allocated to age groups, using the class intervals 0–, 15–, 25–, 35–, 40–, and thence by 5-year groups to a final group of 85 and over. Each annual age group was amalgamated into a quinquennial group. The age specific certification rates for each quinquennium were calculated from these data, and from the Registrar General's "Estimate of Population, Total Males, England and Wales," for the appropriate quinquennia (Registrar General, 1921–50). The equivalent of the Comparative Mortality Index (C.M.I.; Registrar General, 1949), to which we shall refer as the Comparative Certification Index (C.C.I.), was computed from these data with the quinquennium 1936–40 (mid-point 1938) as the base. The crude certification rates were also calculated for these quinquennia. The values are shown in the Table.

Table

CRUDE AND CORRECTED ANNUAL CERTIFICATION RATES PER 10^6 MALES LIVING AT ALL AGES, AND COMPARATIVE CERTIFICATION RATE (C.C.I.) WITH QUINQUENNIUM 1936–1940 AS BASE

Date	1921 to 1925	1926 to 1930	1931 to 1935	1936 to 1940	1941 to 1945	1946 to 1950
Crude Rate ..	42·5	48·9	55·0	59·4	72·2	83·3
C.C.I.	0·9224	0·9792	1·0067	1·0000	1·1288	1·2335
Corrected Rate	54·9	58·2	58·8	59·4	67·1	73·3

The corrected certification rates for the same quinquennia were calculated by multiplying the crude certification rate for the quinquennium 1936–40 by the C.C.I. for the other quinquennia. The age specific certification rates for the pooled data of the 30 years 1921–50 were calculated. These are shown for reference in Fig. 1, but the actual data used are the comparable age specific rates for the basal data.

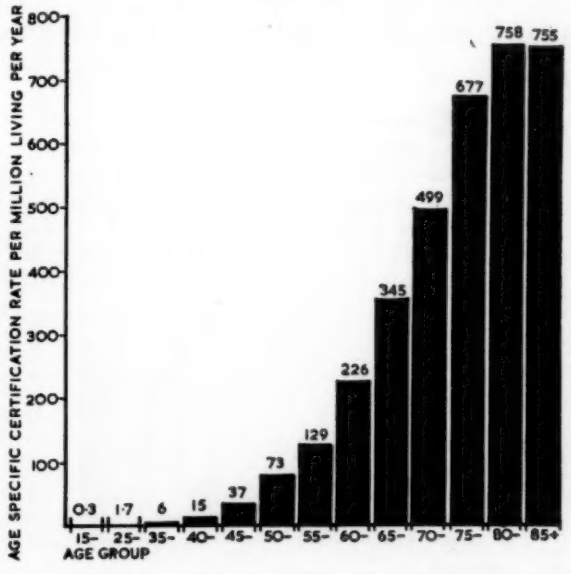

Fig. 1.—All tumours of the bladder. Mean annual age specific certification rate for males in England and Wales, from the pooled data, 1921–50.

The effect of all mortality has been summarized in the British Life Tables and Estimated Life Tables; and the tables for the census years 1921 and 1931, and the estimated table for 1948 were selected as the most appropriate for the present purpose (Registrar General, 1948; 1951). From these life tables and from the bladder tumour data discussed above it was possible to construct tables that would show the expected incidence of death certification in a cohort of given age attenuated by the mean mortality values for England and Wales. This attenuation has, of course, changed with the passing of time.

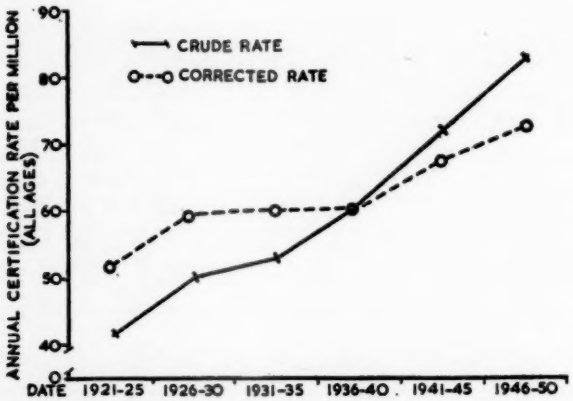

FIG. 2.—All tumours of the bladder. Crude and corrected mean annual certification rates for males in England and Wales, 1921–50.

RESULTS

(1) The crude certification rates and the corrected certification rates are shown in Fig. 2. The two rates are expressed per million males living at all ages per year, and it is apparent that there has been a large increase in the crude certification rate in the last 30 years. When the effects of the changing age structure of the population are removed, a considerable residuum of increase remains. Since there has been little or no improvement in methods of diagnosis of the terminal stages of bladder tumour since the use of the cystoscope became widespread in the early twentieth century, it is suggested that this residual increase is a real increase in the frequency of the condition.

(2) The histogram of the age specific certification rates for the pooled data of the period 1921–50 has already been shown in Fig. 1.

Histograms, with a rather coarser age grouping, for the three decades 1921–30, 1931–40, and 1941–50, are shown in Fig. 3. The pattern is essentially the same in each case, and the real increase of certification discussed above is due to increments of approximately similar proportions in each age group. Furthermore, Fig. 3 shows that no great error is introduced by the assumption of a linear change with respect to time in each age group.

The histogram of the age specific certification rates for the basal data (Fig. 4, opposite) may be regarded as forming a representative pattern for the whole period. The diagram shows the high degree of age specificity, with a fall in rate after the age of 85. This fall, though not relevant to the substance of this paper, is of interest because it suggests that for any intensity of causative stimulus (the sum total of all factors producing, in this case, bladder tumour) there is an immune and a non-immune (in a statistical sense) class of the population. An alteration in the intensity of the causative stimulus might be expected to vary the proportions of these two classes.

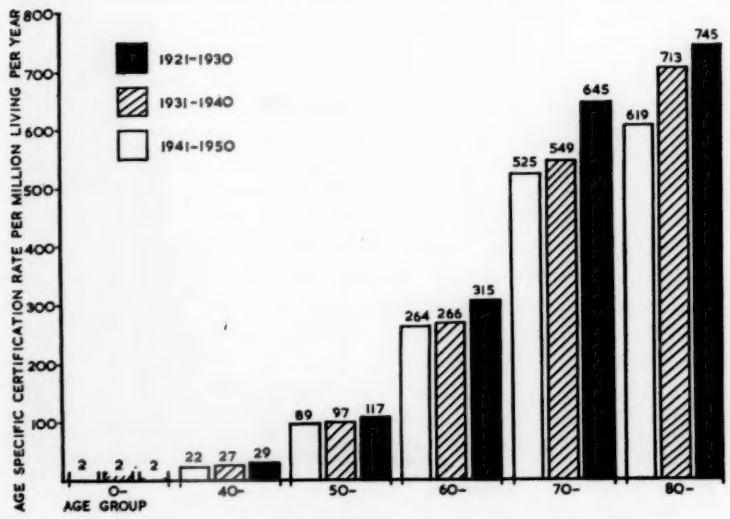

FIG. 3.—All tumours of the bladder. Age specific certification rate for males in England and Wales, for the three decennia, 1921–30, 1931–40, and 1941–50.

(3) The effect of the increasing certification rate and the decrease in mortality from all causes in younger age groups with the passage of time, coupled with the age specificity, will interact to influence the incidence of death certification from bladder tumour in a population considered at different dates.

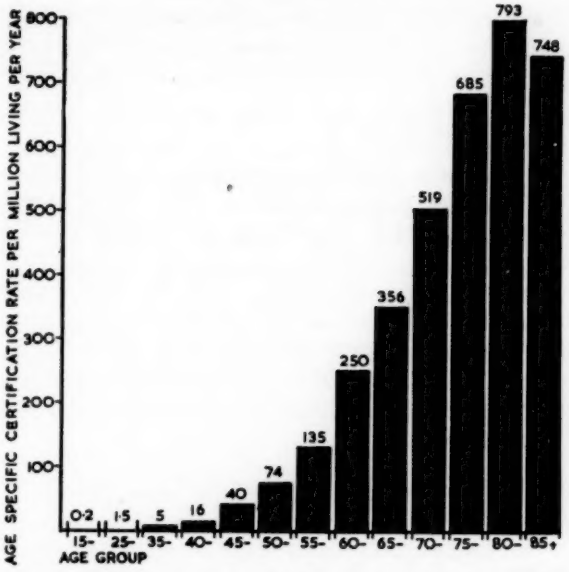

FIG. 4.—All tumours of the bladder. Mean annual age specific certification rate for males in England and Wales, from the basal data for nine years scattered between 1921 and 1950.

Fig. 5 shows this effect for cohorts of initial age 30 considered as being attenuated by all mortality at the risks current in 1921, 1931, and 1948, and acquiring bladder tumour death certificates at the risks prevalent in these years. The whole figure is computed from the death certificates for the 3-year groups 1921–23, 1930–32, and 1947–49, loaded with the life table mortality from the years 1921, 1931, and 1948 respectively. The 1921 table is used because it is based on a census year.

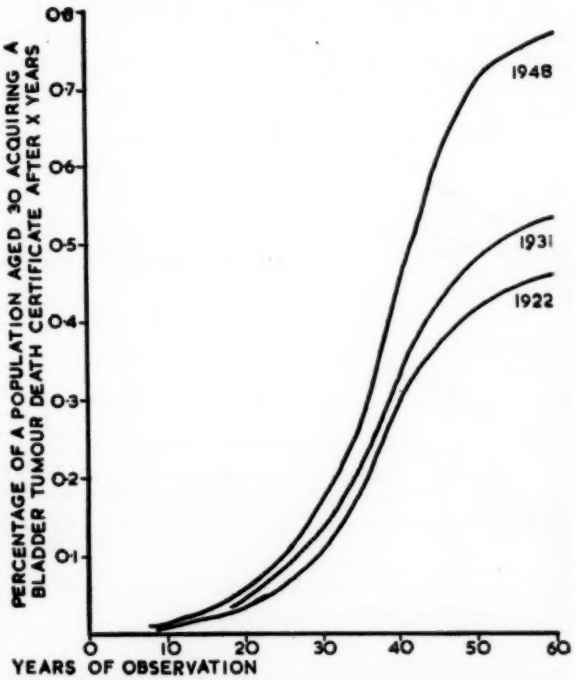

FIG. 5.—Combined effect of changes in certification rate and of all mortality (Males in England and Wales).

The figures for the incidences attained at any stated age are reasonably linear if plotted against date, and have been assumed to be so between the limiting cases, and also for cohorts of initial ages between 20 and 50 years of age.

DISCUSSION

The results reported above show that the incidence of death certification mentioning bladder tumour is highly age specific, and is affected to a considerable degree by contemporaneous conditions.

They also show that there is a marked real increase in the annual corrected certification rate over the last 30 years, an increase which is very unlikely to be due in any large measure to improvement in diagnosis.

The results obtained now allow us to write a series of equations which will give a reasonable estimate of the expected incidence for men entering observation between the ages of 20 and 50, and between the years 1921 and 1950.

Derivation of the Estimating Equations

Required.—An estimate, R, of the incidence of bladder tumour being mentioned on a death certificate, such that R gives the expected value for males at the current mean rate for England and Wales for the date of observation. For convenience, R is to be estimated as the percentage incidence in a theoretical cohort of men, whose age at the time of first observation is Z, and who are observed for x years. The date of the mid-point of the period of observation is w.

Known.—

(1) The age specific certification rates $[M(a.w)]$ at each of n age groups q whose mid-points are a years of age and consisting of C years. $M(a.w)$ is expressed as the rate per million living per year. If the age at the mid-point of the first age group q_1 considered is Z, then a can take the values Z,

$$\left(Z+\frac{C_1+C_2}{2}\right),\left(Z+\frac{C_1+C_2}{2}+\frac{C_2+C_3}{2}\right),\ \ldots$$

$$\left(Z+\frac{C_1+C_2}{2}+\frac{C_2+C_3}{2}\ \ldots+\frac{C_{(n-1)}+C_n}{2}\right)$$

where, as is the case here, C is not necessarily constant, C_1 is the value in the group q_1 whose mid-point is Z, and the last value, C_n, is not finite. The last age group q_n is that class of the population aged over 85 years.

(2) The fraction $({}_1l_Z)$ of an original population observed from birth to the age Z (Registrar General, 1948, 1951) for the years 1921, 1931, and1948. From this the fraction of a population aged Z at first observation surviving to

each of the age groups with mid-point a can be computed from the expression:

$$\left(\frac{1_a}{1_Z}\right)_w,$$

where w = the date of the relevant life table and here can only be 1921, 1931, or 1948.

(3) From the above it has been possible to determine the ultimate frequency of certification in cohorts attenuated by mortality at the rates current in 1921, 1931, and 1948, and acquiring their bladder tumour death certificate at the rates current in these years.

Then.—An estimate $i\,(Z.w.q)$ can be made of the percentage incidence of certification at any age group q_p from the formula:

$$i(Z.w.q) = \sum_{q_1}^{q_p} \frac{C(M.a.w)}{10{,}000}\left(\frac{1_a}{1_Z}\right)_w \quad \ldots\ldots\ldots\ldots (i)$$

which will reach a limiting value, the terminal incidence, $I(Z.w)$ when $q = q_n$, which in this particular case is 85 and over. Thus:

$$I(Z.w) = \sum_{q_1}^{q_n} \frac{C(M.a.w)}{10{,}000}\left(\frac{1_a}{1_Z}\right)_w \quad \ldots\ldots\ldots\ldots (ii)$$

This value $I(Z.w)$ cannot be exceeded because 1_a becomes zero after $q = 85+$. However, since the age group $q = 85+$ has an indeterminate mid-point, the value $I(Z)$ cannot be regarded as a special case of $i(Z)$, but only as its upper limit.

By a possibly fortuitous combination of circumstances, the values of $i(Z.b.q)$ determined from the basal data for the values of $Z = 20$, 30, 40, and 50, and $X = 2{\cdot}5$, $7{\cdot}5$, $12{\cdot}5$ . . . , and the age groups 15–, 25–, 35–, 40–, 45 . . . –75, –80, –85 +, using the Life Table 1 values for 1931, form a nest of cumulative normal curves (Fig. 6), which may be transformed by the use of the normal deviate to a series of straight lines, equidistant at $X = 0$ and almost parallel (Fig. 7), which are described by the equation:

$$Y(b.Z.X) = -0{\cdot}80 + 0{\cdot}08119X + (0{\cdot}0800 + 0{\cdot}0004X)Z \quad \ldots\ldots\ldots\ldots\ldots\ldots (iii)$$

where $Y(b.Z.X)$ = Probit of $[i(Z.b.X)$ expressed as a percentage of $I(Z.b)]$.

The standard error of estimate of $Y(b.Z.X) = \pm 0{\cdot}107$.

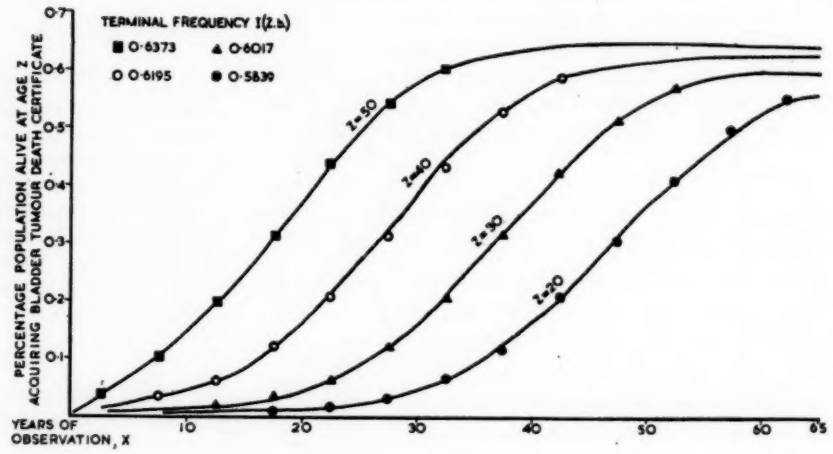

FIG. 6.—Observed values of $i\,(Z.b.q)$ fitted with calculated integrated normal curves for $Z = 20$, 30, 40, 50, and values of X from 2 to 65.

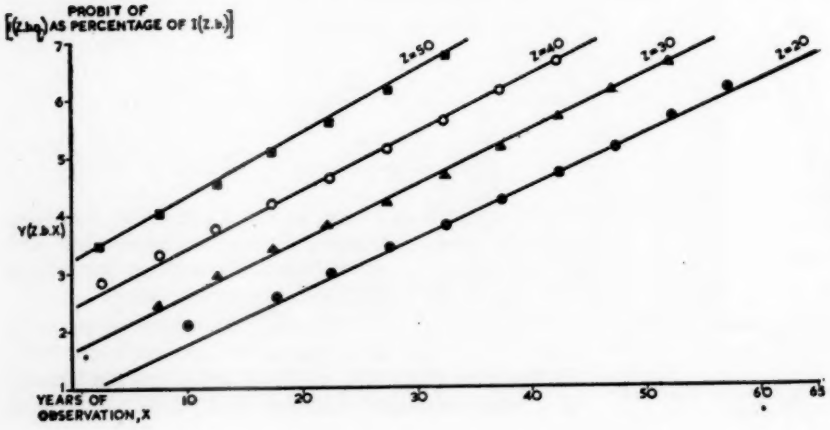

FIG. 7.—Observed values of $Y\,(Z.b.q)$ fitted with calculated probit-transformed integrated normal curves described by the equation $Y(Z.b.X) = -0{\cdot}80 + 0{\cdot}08119X + (0{\cdot}080 + 0{\cdot}0004X)Z$.

The probit (the deviate + 5) is used because it is a well tabulated function, and the Tables are found in standard works on medical statistics (*e.g.* Fisher and Yates, 1948).

The values of $I(Z.b)$ for $Z = 20$, 30, 40, and 50 form a linear series which may be described by the equation:

$$I(Z.b) = 0{\cdot}5483 + 0{\cdot}00178Z \quad \ldots\ldots\ldots\ldots\ldots\ldots (iv)$$

The standard error of estimate = 0·0028.

Furthermore it is observed that the values of $I(Z.w)$ for $Z = 30$, $w = 1921$, 1931, and 1948, and where $M(a.w)$ is based on figures for the triennia 1921–23, 1930–32, and 1947–49 respectively, form a linear regression which may be described as:

$$I(30.w) = I(30.1921) + 0{\cdot}0019\ (w - 1921) \quad \ldots\ldots (v)$$

and it is assumed that this expression is valid for values of Z between 20 and 50. From this it may be calculated that $I(Z.b) = I(Z.1935)$. Thus, an estimate $[\bar{I}(Z.w)]$ of $I(Z.b)$, adjusted for the effects of contemporaneous conditions, may be obtained from the expression:

$$\bar{I}(Z.w) = I(Z.b) + 0{\cdot}0119\ (w - 1935) \quad \ldots\ldots\ldots (vi)$$

which becomes:

$$\bar{I}(Z.w) = 0{\cdot}5483 + 0{\cdot}00178Z + 0{\cdot}0119\ (w - 1935).$$

The whole expression may now be written:

$$R(Z.w.X) = [\text{Anti-probit } Y(b.Z.X)\ 0{\cdot}5483 + 0{\cdot}00178Z + 0{\cdot}0119\ (w - 1935)] \div 100 \quad \ldots\ldots\ldots\ldots\ldots\ldots\ldots (vii)$$

where $Y(b.Z.X)$ = Probit of $[i(Z.b.X)$ as a percentage of $\bar{I}(Z.w)]$.

The standard error of estimate is ± 0·0169 as determined from the residuals from the $i(Z)$ values for the three triennia 1921–23, 1930–32, and 1947–49 at the values of X and Z already used for the basic data. This gives a total of 111 observations, and the standard error of estimate, adjusted for this number of observations, becomes ± 0·0171.

Use of the Equations.—The final estimate (T) of the expected number of death certificates for a class of men defined by environment, but entering the environment at different ages and different times, is given by:

$$T = \sum \frac{R(Z.w.X) \times P(Z.w - \frac{X}{2})}{100} \pm$$

$$0{\cdot}00017 \sum P(Z.w - \frac{X}{2}) \quad \ldots\ldots\ldots\ldots (viii)$$

for all the observed paired values of Z and w, where P = the number of persons entering observation at age Z, w = the date of the mid-point of the period for which they are observed, and X = the period of observation.

Equation (*vii*) may be re-written:

$$R(Z.w.X) = \frac{\bar{I}(Z.w) \times \text{Anti-probit } Y(b.Z.X)}{100},$$

and tables of $\bar{I}(Z.w)$ and Antiprobit $Y(b.Z.X)$ can be constructed.

For most practical purposes, T may be used as the final estimate without its standard error of estimate, which is fairly small.

Summary

The effects of age and contemporaneous conditions upon the frequency of death certificates mentioning tumour of the bladder are discussed for data relating to males in England and Wales between the years 1921 and 1950.

It is shown that the age-specific annual certification rate increases greatly with advancing age until 80 years, after which it drops.

It is also shown that not only is the crude annual certification rate for all ages increasing, but that the corrected annual certification rate, after adjusting for changes in age composition of the population, shows a marked increase. These rates were calculated as mean values of quinquennia.

These observations are used to calculate a series of equations which will give a close estimate of the expected rate of death certification of bladder tumour in a male population subjected to the mean "risk" pertaining in England and Wales. These equations will allow for the age composition of the population observed and for the time at which it was observed.

The equations should be useful in allowing industrial concerns to form a reasonably reliable estimate of the expected rate of the mention of bladder tumour on death certificates of their members or ex-members, and hence to form a basis for comparison with the number they actually find. This should help in assessing environmental risk.

This work was carried out as part of the programme of a research scheme under the auspicies of the Association of British Chemical Manufacturers.

Miss Drever B. McDonald sorted many years of death certificates into their age groups, and Miss Margery E. Hosker and Miss Joan T. Pearson compiled the alphabetical index of death certificates, and it is a pleasure to acknowledge this assistance.

Thanks are also due to Dr. E. R. A. Merewether, Chief Medical Officer, Ministry of Labour and National Service, for placing most of the death certificates at our disposal, and to the General Register Office for the remaining certificates and for much other help.

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Brit. J. prev. soc. Med. (1953), 7, 20–23

BIRTH WEIGHTS OF SOUTH AFRICAN BABIES

IV. ASSOCIATION WITH MATERNAL AGE

BY

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This paper is a report on the association between birth weight and age of mother. Previous communications have dealt with the effects on birth weight of race, sex, birth rank, and season of birth (Salber and Bradshaw, 1951a, b; 1952).

Material and Methods

The data were collected from various hospitals and nursing homes in Durban, Pietermaritzburg, and Cape Town (as previously described), the numbers considered here being 3,164 European, 1,059 Coloured, 2,188 Bantu, and 1,391 Indian babies. As before, abortions and multiple births were excluded, but in determining the birth rank of the child, abortions were included.

In view of the close relationship between age of mother and birth rank of child, an attempt was made to assess the association of birth weight specifically with each of these variables:

(*i*) by determining the mean birth weight for each maternal age group within each birth rank,

(*ii*) by recourse to analysis of variance.

The maternal age was taken in 5-year groups from 15 to 35 +. Birth ranks were classified 1, 2, 3, and 4 +. All calculations are for sexes combined, as no significant differences were found between boys and girls.

Results

(1) *Examination of Sub-Group Means.*—The mean birth weight, with standard deviation, for each birth rank in each maternal age group, is shown in Table I (opposite) for the four ethnic groups. There is a steady rise in birth weight with increasing rank, when all maternal ages are grouped; and this trend is also discernible within each maternal age. When all ranks are combined, association of birth weight with age of mother is not consistent: in the Europeans virtually no difference is found from age to age; in the Coloured and Bantu groups, birth weight appears to increase until the maternal age 30–34 years, with a slight drop in the highest age-group; in the Indian group, there is a steady rise in birth weight with increasing age. When each birth rank is considered separately the following facts may be noted as age increases:

(*a*) among first-born Europeans, weight decreases;

(*b*) among first-born Coloured, Bantu, and Indians, weight increases;

(*c*) among births after the first, weight shows no consistent trend in any of the four groups.

(2) *Analysis of Variance.*—The data were first tested for homogeneity by the procedure described by Kendall (1947), by setting out the mean weights separately for each racial group, as a one-way classification with twenty classes (*i.e.* four birth ranks and five maternal age groups). The variance of the means of the classes and the "residual variance" (*i.e.* that obtained from the pooled data within the twenty classes) were obtained, giving two separate estimates of population variance in birth weight. The significance of the ratio of these was tested by Snedecor's *F*-test. For each ethnic group the difference was significant at the 1 per cent. level, indicating that the data are not homogeneous, *i.e.* variations in birth rank and maternal age together account for a significant proportion of variation in birth weight.

The data were then arranged as a two-way classification:

(*i*) An estimate of population variance was

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TABLE I

MEAN BIRTH WEIGHT ACCORDING TO MATERNAL AGE AND BIRTH RANK

Racial Group	Maternal Age	Birth Rank														
		1			2			3			4+			All Ranks		
		No. of Births	Mean Weight (lb)	S.D.	No. of Births	Mean Weight (lb)	S.D.	No. of Births	Mean Weight (lb)	S.D.	No. of Births	Mean Weight (lb)	S.D.	No. of Births	Mean Weight (lb)	S.D.
European	15–19	103	7·52	1·01	8			1						112	7·51	1·02
	20–24	686	7·41	1·10	216	7·61	1·21	34	7·24	1·07	5			941	7·46	1·13
	25–29	479	7·32	1·18	403	7·70	1·09	140	7·80	1·26	29	7·84	1·23	1,051	7·54	1·18
	30–34	197	7·15	1·10	258	7·70	1·09	152	7·80	1·01	64	7·88	1·53	671	7·58	1·16
	35+	85	7·09	1·14	128	7·38	1·24	103	7·74	1·18	73	7·81	1·14	389	7·49	1·21
	All Ages	1,550	7·34	1·13	1,013	7·64	1·14	430	7·74	1·15	171	7·86	1·31	3,164	7·52	1·16
Coloured	15–19	168	6·53	1·06	39	6·52	0·85	7						214	6·50	1·04
	20–24	169	6·63	1·04	136	6·90	1·19	56	7·34	1·00	30	6·93	1·60	391	6·84	1·16
	25–29	43	6·88	1·33	54	6·83	1·03	44	6·99	1·05	89	7·20	1·24	230	7·01	1·19
	30–34	11			21	7·44	0·88	15			74	7·51	1·51	121	7·43	1·32
	35+	3			5			6			89	7·29	1·54	103	7·27	1·50
	All Ages	394	6·63	1·09	255	6·90	1·12	128	7·08	1·08	282	7·29	1·46	1,059	6·93	1·23
Bantu	15–19	220	6·64	1·06	46	6·65	1·30	3						269	6·65	1·10
	20–24	382	6·74	0·95	321	6·96	1·07	130	7·14	1·07	62	7·08	1·56	895	6·90	1·07
	25–29	91	6·99	0·86	156	7·12	1·13	181	7·24	1·11	219	7·40	1·24	647	7·23	1·14
	30–34	5			35	7·02	1·23	38	7·12	0·94	172	7·29	1·22	250	7·23	1·18
	35+	3			4			8			112	7·19	1·09	127	7·18	1·05
	All Ages	701	6·75	0·98	562	6·99	1·13	360	7·19	1·07	565	7·29	1·25	2,188	7·02	1·11
Indian	15–19	197	6·19	1·04	53	6·33	1·26	13			5			268	6·22	1·07
	20–24	168	6·20	0·95	153	6·44	1·07	109	6·58	0·99	100	6·78	1·15	530	6·45	1·05
	25–29	32	6·39	0·95	41	6·60	1·04	41	6·57	1·03	202	6·73	1·42	316	6·66	1·29
	30–34	6			12			11			135	6·72	1·47	164	6·65	1·41
	35+	1			2			1			109	6·91	1·33	113	6·88	1·33
	All Ages	404	6·20	0·99	261	6·43	1·11	175	6·55	0·96	551	6·77	1·36	1,391	6·51	1·19

TABLE II

Racial Group	Variable	*F*	Degrees of Freedom		Level of significance of contribution to total variance due to variable (per cent.)
			Greater Mean Square	Lesser Mean Square	
European	Maternal Age	1·19	4	3,145	Less than 5
	Birth Rank	10·67	3	3,145	1
Coloured	Maternal Age	3·93	4	1,040	1
	Birth Rank	3·22	3	1,040	5
Bantu	Maternal Age	2·89	4	2,169	5
	Birth Rank	2·33	3	2,169	Less than 5
Indian	Maternal Age	1·31	1,371	4	Less than 5
	Birth Rank	3·45	3	1,371	5

obtained, unbiased by birth rank, assuming homogeneity of birth-weight data with respect to maternal age. The significance of the ratio between this and the independent residual variance obtained previously was tested as before. When this is significant, maternal age *per se* is presumed to introduce a significant degree of heterogeneity into the data.

(*ii*) This procedure was repeated with the appropriate substitutions to determine the significance of heterogeneity in birth-weight data due to birth rank *per se*. Results of this analysis are given in Table II.

By the method of least squares, parameters were estimated (Table III, overleaf) representing the expected deviation due specifically to maternal age or to birth rank of any particular birth weight from the population mean. These parameters serve as indices summarizing, on a comparative basis, the

TABLE III

(*a*) PARAMETERS ESTIMATING ASSOCIATION OF BIRTH RANK WITH BIRTH WEIGHT

Birth Rank	Racial Group			
	European	Coloured	Bantu	Indian
1	−0·36	−0·23	−0·22	−0·25
2	−0·02	−0·05	−0·06	−0·05
3	+0·11	+0·11	+0·09	+0·05
4+	+0·27	+0·17	+0·19	+0·24

(*b*) PARAMETERS ESTIMATING ASSOCIATION OF MATERNAL AGE WITH BIRTH WEIGHT

Maternal Age	Racial Group			
	European	Coloured	Bantu	Indian
15–19	+0·16	−0·31	−0·19	−0·10
20–24	+0·04	−0·08	−0·03	−0·02
25–29	+0·02	−0·03	+0·16	+0·02
30–34	−0·04	+0·31	+0·08	−0·05
35+	−0·18	+0·10	−0·01	+0·14

direction and degree of influence on birth weight of each of the two variables.

Table III*a* shows that birth weight rises steadily with increasing birth rank, independently of maternal age. An interesting feature of Table III*b* is that the European and Non-European patterns are diametrically opposed up to the 25–29 age group. In the European group, birth weight tends to be highest for the young mothers, and to drop steadily with increasing age. In the Non-European groups, birth weight is in general lowest for the young mothers and rises in all three groups to the 25–29 year group. After this the trend is inconsistent; but it appears that among Non-Europeans, mothers of 35+ tend to have heavier babies than young mothers, whereas among Europeans, babies born to mothers of 35+ are much lighter than those of young mothers.

DISCUSSION

There is little published information about the association of age of mother with birth weight.

Duncan (1864) and Griffith and Gittings (1907) stated that the heaviest babies were born to mothers age 25–29. These authors did not assess the separated associations of birth weight with age of mother and birth rank.

Donald (1939) stated that:

> age of mother had no apparent effect on the weight of first-born children, but may have had a slight influence on second-born children, mothers about 30 years old having the heaviest.

Uttley (1940), investigating the weights of Chinese babies, stated:

> the older the mother, the heavier is the baby.

But in his results ranks were combined, and no consistent relationship was apparent on examination of his data for each rank separately.

McKeown and Gibson (1951) concluded that:

(*a*) Weight increases with parity.

(*b*) There is no consistent association between weight and maternal age when birth rank is fixed.

Solth and Abt (1951), working on a German and Swiss population over the last 50 years, found that:

> mean birth weight increases with age of mother up to 35 years, and then decreases slightly. The increase is in both primiparae and multiparae. Of the three factors, age of mother, parity, and sex of child, parity has the greatest effect on birth weight.

Karn and Penrose (1951) found that birth weight increases with parity, but decreases slightly with mother's age.

The differences between European and other groups in the association of birth weight with maternal age, to which we have drawn attention, may be in part due to the likelihood that influences of maternal age and birth rank are not strictly additive, but depend on their inter-relationship. In this connexion it is of some interest to record that the product-moment coefficient of correlation between age of mother and birth rank was found to be relatively low in Europeans (+0·46 as against +0·72, +0·72 and +0·77 for Coloured, Bantu, and Indian groups respectively).

SUMMARY

(1) Birth weights of infants were studied with special reference to association specifically with age of mother. The material comprised 3,164 European, 1,059 Coloured, 2,188 Bantu, and 1,391 Indian babies.

(2) When age of mother is fixed, there is a steady increase in birth weight with increasing rank in all racial groups.

(3) When rank is fixed, as age increases the following facts are apparent:

(*a*) among first-born Europeans, weight decreases;

(*b*) among first-born Coloured, Bantu, and Indians, weight increases;

(*c*) among births after the first weight shows no consistent trend in any of the four groups.

(4) The correlation between age of mother and birth rank is much higher for the three non-European groups than for the Europeans.

We wish to thank Dr. S. L. Kark, Medical Officer-in-Charge, Institute of Family and Community Health, for his advice and interest, and Prof. P. Stein and Mr. S. E. Cruise, Department of Mathematics, Natal University, for statistical advice. We are again indebted to the staffs of the various hospitals who placed their records at our disposal.

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Brit. J. prev. soc. Med. (1953), 7, 24–25

INCIDENCE OF HAEMOLYTIC DISEASE OF THE NEWBORN IN THE OFFSPRING OF SISTERS

BY

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Haemolytic disease of the newborn most commonly occurs when an Rh-negative mother has been sensitized to the *D* antigen, either from an Rh-positive foetus during pregnancy, or by an injection or transfusion of blood. Sensitization, however, occurs much less commonly than is theoretically possible; and Wiener (1946) has suggested that the ability of an individual to become sensitized is conditioned by a certain constitutional factor, *K*, as well as by exposure to a foreign antigen. He suggests that homozygous *KK* individuals (0·02 per cent. of the population) respond readily to antigenic stimuli, that heterozygous *Kk* individuals (3 per cent. of the population) are moderately easy to sensitize, and that homozygous *kk* individuals (97 per cent. of the population) are difficult to sensitize. If such a constitutional factor is operative, haemolytic disease of the newborn might be expected to arise with greater frequency in the offspring of women whose sisters had had children with haemolytic disease.

The measure of this effect may be computed as we show below. If we assemble particulars of the sisters of women (*Index* Cases) whose children have been affected by haemolytic disease of the newborn, then, since each Index Case is *ipso facto* Rh-negative, the sisters of Index Cases will include more Rh-negative individuals than a random sample of women. We may calculate the expected proportion of Rh-negative individuals among sisters of Index Cases and thence the expected proportion of their children affected with haemolytic disease, as follows:

let d = recessive gene frequency (of *d*-gene),
so that $1-d$ = dominant gene frequency (of *D*-gene).

Recessive individuals may arise only from the three matings:

Type of Mating	Frequency of Mating	Proportion of Recessive Offspring	Frequency of Recessive Offspring
A R × R	d^4	1	d^4
B H × R	$4d^3(1-d)$	$\frac{1}{2}$	$2d^3(1-d)$
C H × H	$4d^2(1-d)^2$	$\frac{1}{4}$	$d^2(1-d)^2$

where R = Homozygous recessive; H = Heterozygote.

Thus a recessive individual results from the three mating groups (denoted above as A, B, C) in the relative proportions $d^2 : 2d(1-d) : (1-d)^2$. Sibs of such an individual will also be recessive in the same proportions as above, *i.e.* as $1 : \frac{1}{2} : \frac{1}{4}$.

The total frequency of all recessive offspring of the matings from which recessive offspring may come is:

$$d^4 + 2d^3(1-d) + d^2(1-d)^2 = d^2.$$

Hence the mean proportion of sibs of Index Cases (*i.e.* known recessives) expected also to be recessive is:

$$d^2 + d(1-d) + \tfrac{1}{4}(1-d)^2 = \tfrac{1}{4}(1+d)^2,$$

wherein the assumptions we have made are that the Index Cases result from families A, B, C, in the randomly expected proportions, and that the size of a sibship bears no relation to whether it is of type A, B, or C.

Now those sisters of Index Cases who are recessive may marry Rh-positive men, when the circumstances would be propitious for the production of haemolytic disease. There will be a proportion $(1-d)^2$ of homozygous Rh-positive males all of whose children will be Rh-positive, and a proportion $2d(1-d)$ of heterozygous males, half of whose children by an Rh-negative woman will be Rh-positive. Thus the proportion of Rh-positive children to be expected if the Rh-negative sisters of Index Cases marry at random with respect to the Rh gene is:

$$(1-d)^2 + d(1-d) = (1-d),$$

and the proportion of Rh-positive children of Rh-negative mothers which is expected among the children of sisters of Index Cases is:

$$\tfrac{1}{4}(1+d)^2(1-d),$$

if we may assume that the number of children per family is sensibly unaffected by their Rh genotype.

It has been observed that in general a proportion p (about 5 per cent.) of Rh-positive children born to Rh-negative mothers will show signs of icterus gravis, so that the proportion of the children of sisters of Index Cases expected to be affected is:

$$\tfrac{1}{4}p(1-d)(1+d)^2$$

If however, Wiener's hypothesis of an inherited factor of enhanced susceptibility is operative, we proceed as follows.

If we assume that an Index Case possesses at least one dominant gene K, of frequency x, her parents' mating types may be:

Type of Mating	Frequency of Mating	Proportion of Offspring of Dominant Phenotype	Frequency of Dominant Offspring
R × H	$4x(1-x)^3$	$\frac{1}{2}$	$2x(1-x)^3$
H × H	$4x^2(1-x)^2$	$\frac{3}{4}$	$3x^2(1-x)^2$
R × D	$2x^3(1-x)^2$	1	
H × D	$4x^3(1-x)$	1	$x^3(2-x)^2$
D × D	x^4	1	

where R = Homozygous recessive (kk)
H = Heterozygote (Kk)
D = Homozygous dominant (KK)

Again, the sibs of such an Index Case will also carry at least one dominant gene in the same proportions as above. Thus the frequency of pairs of sisters, each carrying a dominant gene, is obtained from the product of the last two columns, and is:

$$p_1 = \tfrac{1}{4}x(4 + 5x - 6x^2 + x^3).$$

The proportion of the general population who carry at least one dominant gene K is:

$$p_2 = 1 - (1-x)^2 = x(2-x),$$

so that the probability, relative to the general population frequency, of a sister's carrying a gene is:

$$\frac{p_1}{p_2} = \tfrac{1}{2} + \tfrac{7}{8}x,$$

and this is the proportion of sisters of Index Cases who also carry the factor K.

The estimate of Wiener (1946) is 3 per cent. for heterozygous K individuals, yielding approximately 0·015 for x, so that $\frac{p_1}{p_2}$ is about 51 per cent.

Thus of the proportion $\frac{1}{4}(1+d)^2(1-d)$ of susceptible offspring of sisters of Index Cases, those actually affected with haemolytic disease will be:

(*i*) approximately 5 per cent., if the chance is random,

(*ii*) approximately 51 per cent., on Wiener's postulate of a simple dominant gene K conferring an enhanced susceptibility.

Thus Wiener's postulate leads to a proportion of affected which is about ten times greater than that expected in the absence of a dominant familial predisposition. This is of course on the assumption of independence of the d-gene and the K-gene. Linkage might increase the proportion by as much as about 40 per cent.

To test the merits of alternative hypotheses, we have made use of the cases of icterus gravis treated at the Children's Hospital, Birmingham, between 1920 and 1947, recently reviewed by one of us (Gerrard, 1951). Because the likelihood of occurrence of *iso*-immunization is reduced in small families, and to allow of the inclusion of a greater proportion of younger sisters' families, we have drawn chiefly from the older mothers in the series. Through them we have obtained details of the families of their sisters, the numbers of children, and the numbers who were deeply jaundiced in infancy. We obtained the required details from 111 Index Cases of the series, and in five instances one sister, in a sixth, two sisters, had had children who were severely jaundiced as infants. The 111 Index Cases had a total of 274 sisters who had 566 children. Eleven of these children were severely jaundiced in infancy, and in at least nine of these the jaundice was due to Rh *iso*-immunization.

The expected number of cases is 8·3 calculated according to (*i*), and 85·4 according to (*ii*). This series therefore lends no support to the postulate of a genetic factor facilitating sensitization such as Wiener has proposed; indeed the close accord between the number observed and that expected in the absence of the factor K suggests that the greater susceptibility to sensitization which some Rh-negative women display is distributed independently and is attributable to some environmental agency. For any other condition facilitating *iso*-immunization, whether directly improving antigenic response or increasing the permeability of the placenta, if dependent on a single gene substitution, would increase the proportion affected among the offspring of sisters from the 5 per cent. rate of (*i*) to a minimum of 25 per cent., as a recessive with full penetrance.

SUMMARY

Observations on the occurrence of haemolytic disease of the newborn in the offspring of sisters are used to show, by their close agreement with genetic expectation on the assumption of random distribution of susceptibility, that any hypothesis of a simply-inherited factor which facilitates sensitization is improbable.

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Brit. J. prev. soc. Med. (1953), 7, 26–30

INVESTIGATION OF THE NEED FOR PHYSICAL TREATMENT DURING PROLONGED ABSENCE FROM WORK

BY

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In 1949 a Ministry of Health circular [R.H.B. (49)36] attempted to define the responsibility of the National Health Service in relation to prevention and limitation of disability. It was stated that:

> the Ministry of Labour's Resettlement Services.... deal with the terminal disability arising from earlier sickness or injury, and do not begin until disability is established.

and that the Health Service should make adequate provision prior to that stage, in order to reduce

> the large number of patients whose prolonged and ill-directed convalescence.... causes so much absenteeism and often sows the seeds of a permanent disability neurosis.

For this purpose the circular suggested that hospital rehabilitation services should be expanded, and should include physiotherapy departments, remedial gymnasia, and occupational therapy rooms.

Responsibility for these services falls mainly upon Regional Hospital Boards. The Boards are, however, finding it difficult to finance expansion of the traditional services, and require to know whether the cost of extending the rehabilitation services will be justified. According to the Ministry circular, experience has shown that:

> early measures of rehabilitation, combined with expert guidance through convalescence, produce striking results in the recovery of fitness, the reduction of permanent disability, and the shortening of time off work.

No evidence is quoted in support of this statement, and no estimate is given of the cost of the services, or of the extent of the expansion required.

The present investigation was undertaken to provide information on some of these matters for the guidance of the Birmingham Regional Hospital Board. We have attempted to assess the incidence of prolonged absence from work, and have enquired with only partial success, to what extent expansion of rehabilitation services might be expected to contribute to the welfare of patients and to reduction of the period of absence.

Material

As it was not our purpose to explore absenteeism in general, upon which there is already a considerable literature, we confined our attention to the two groups most likely to benefit from physical treatment:

(*a*) patients admitted to hospital,

(*b*) patients not admitted to hospital but who were absent from work for a considerable period.

The two groups were readily identified by taking all patients absent 28 days or more, since a small preliminary enquiry had indicated that employees absent for less than a month had rarely been in hospital, and that very few of them required physical treatment which they had not received.

The enquiry was conducted through the works' medical officers of six large firms (the smallest had more than 2,000 employees), which together employed 20,677 men and 9,809 women. These firms were engaged in both light and heavy industry, and provided a wide variety of occupations. The medical officers interviewed on return to work all absentees who had left work because of illness or accident between October 1, 1950, and September 30, 1951, and had been absent for 28 or more consecutive days. A record card completed for each absentee covered the following principal points:

(*a*) duration of absence (divided, for patients admitted to hospital, into periods before admission, in hospital, and after discharge);

(*b*) medical cause of absence as indicated by general practitioner's certificate and patient's statement;

(*c*) identification by the medical officers of patients considered to have required out-patient physical treatment or admission to a convalescent home during their absence, with details of services actually received.

Since the enquiry was restricted to firms with a well-developed medical service, results are to some extent unrepresentative. Five of the six firms provide infra-red and ultra-violet light treatment (at one firm massage, wax baths, and a full range of galvanic, faradic, and sinusoidal therapy are available) and two have their own convalescent homes; it is therefore probable that the need for these services is greater than the results suggest. Moreover there is reason to believe that the incidence of prolonged absence was underestimated, first because

some absentees who returned to work were undoubtedly missed, and second, because no allowance was made for workers who had not returned 6 months after the completion of the enquiry.

Incidence of Prolonged Absence

Of the 30,486 employees, 5·2 per cent. (1,576) left work during the year, because of sickness or accident, and were absent for 28 or more consecutive days; 1·4 per cent. (427) had been admitted to hospital. As indicated above, the incidence of prolonged absence was somewhat higher than these figures suggest; in one firm 9·8 per cent. of the employees were absent for at least a month, and 2·9 per cent. had been admitted to hospital.

The mean duration of absence was 66 days for all absentees, and 83 and 60 days for persons admitted and not admitted to hospital respectively. The difference between the means for the two sexes was trivial.

Table I gives the percentage distribution of absentees according to duration of absence. Two in every five employees admitted to hospital were away from work for 3 months or more, and the incidence of prolonged absence was also quite high among persons not admitted to hospital.

Table II explores the association between absenteeism and age; not all firms were able to give the age distribution of their employees and the data are derived from the experience of 11,484 men and 7,910 women. The incidence of prolonged absence rises rapidly with age; this is mainly due to the association between incidence and age in patients not admitted to hospital, and more particularly in patients not attending hospital out-patient departments (see Figure, below).

Table I*

PERCENTAGE DISTRIBUTION OF ABSENTEES ACCORDING TO DURATION OF ABSENCE

Patients	Duration of Absence (wks)				
	4–	8–	12–	16 and over	Total
Admitted to hospital	32·6	27·4	18·7	21·3	(427) 100 per cent.
Not admitted to hospital	60·6	23·4	9·7	6·3	(1,149) 100 per cent.

Numbers of absentees are given in brackets.

* With the exception of Table II, the Tables are based on the experience of 30,486 employees (20,677 males and 9,809 females).

Table II

PERCENTAGE OF EMPLOYEES ABSENT, BY AGE AND SEX

Sex	Age (yrs)					
	15–	25–	35–	45–	55 and over	All Ages
Male ..	1·4 (22)	2·7 (69)	4·2 (112)	7·5 (188)	11·6 (245)	5·5 (636)
Female	1·9 (52)	3·5 (69)	5·1 (82)	7·1 (93)	6·5 (25)	4·0 (321)

This Table is based on the experience of 11,484 male and 7,910 female employees of known age.

Assessment of Patients' Need for Physical Treatment and Convalescence

As stated above, the works' medical officers recorded details of physical treatment received by patients not admitted to hospital, and by hospital patients after discharge; they attempted to assess whether patients who had not received physical treatment would have benefited from it, and Table III (overleaf) shows their findings. Some form of physical therapy had been received by 8·7 per cent. of patients, and it was considered that a further 7·3 per cent. would have benefited from treatment but had not received it. The services appear to be reasonably adequate for patients discharged from hospital, but it was considered that 9 per cent. (103) of the patients not admitted to hospital might have benefited from treatment

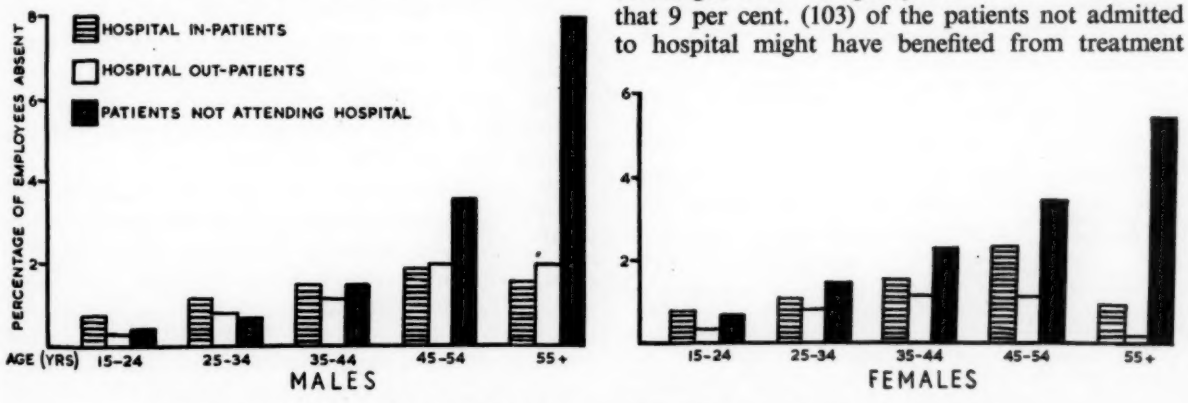

FIGURE.—Incidence of absenteeism distributed by age and sex, and by type of hospital treatment received.

TABLE III

PATIENTS CONSIDERED TO HAVE REQUIRED OUT-PATIENT PHYSICAL TREATMENT

Patients	Physical Treatment			Total
	Considered Necessary		Considered Unnecessary	
	Received	Not Received		
Admitted to hospital ..	14·1 (60)	2·8 (12)	83·1 (355)	100 per cent. (427)
Not admitted to hospital	6·7 (77)	9·0 (103)	84·3 (969)	100 per cent. (1,149)
Total ..	8·7 (137)	7·3 (115)	84·0 (1,324)	100 per cent. (1,576)

which they had not received. Table IV gives the diagnosis in these cases, most of which are of a kind usually considered suitable for physical therapy.

TABLE IV

DIAGNOSIS IN PATIENTS WHO MIGHT HAVE BENEFITED FROM OUT-PATIENT PHYSICAL TREATMENT BUT DID NOT RECEIVE IT

Diagnosis	Patients		Total
	Admitted to Hospital	Not Admitted to Hospital	
Lumbago and Sciatica	—	38	38 (33·0)
Arthritis	—	13	13 (11·3)
Rheumatism, Fibrositis, and Neuritis ..	—	24	24 (20·9)
Injuries	5	20	25 (21·7)
Other conditions ..	7	8	15 (13·0)
Total	12	103	115 (100 per cent.)

The medical officers considered that about one-third (510) of the absentees should have been sent to convalescent homes; less than one-sixth (229) had in fact been admitted (Table V).

TABLE V

PATIENTS CONSIDERED TO HAVE REQUIRED ADMISSION TO A CONVALESCENT HOME

Patients	Convalescent Home			Total
	Considered Necessary		Considered Unnecessary	
	Admitted	Not Admitted		
Admitted to hospital ..	27·2 (116)	18·3 (78)	54·6 (233)	100 per cent. (427)
Not admitted to hospital	9·8 (113)	17·7 (203)	72·5 (833)	100 per cent. (1,149)
Total ..	14·5 (229)	17·8 (281)	67·6 (1,066)	100 per cent. (1,576)

The need is not confined to those who had not been in hospital, and 18 per cent. of hospital in-patients were thought to require a period of convalescence which had not been arranged. Table VI shows the type of patient who might have benefited from convalescence: about two-thirds of the hospital patients were recovering from operations and more than half of those not admitted to hospital had respiratory diseases.

TABLE VI

DIAGNOSIS IN PATIENTS WHO MIGHT HAVE BENEFITED FROM ADMISSION TO A CONVALESCENT HOME BUT WERE NOT ADMITTED

Diagnosis	Patients		Total
	Admitted to Hospital	Not Admitted to Hospital	
Bronchitis (acute and chronic)	—	48	48 (17·1)
Pneumonia	8	26	34 (12·1)
Influenza	—	38	38 (13·5)
Peptic ulcer	6	17	23 (8·2)
Post-operative debility	48	—	48 (17·1)
General debility ..	—	20	20 (7·1)
Other conditions ..	16	54	70 (24·9)
Total	78	203	281 (100 per cent.)

EFFECT OF IMPROVED SERVICES ON THE DURATION OF ABSENCE

We now enquire to what extent improved rehabilitation services may reduce the period of absence.

(*a*) PATIENTS ADMITTED TO HOSPITAL.—For patients admitted to hospital the period of absence can be divided into periods before admission, in hospital, and after discharge. The mean durations of these intervals are 8, 21, and 54 days respectively. We are here concerned mainly with the periods before admission and after discharge, but it may be noted that 21 days is a little longer than the mean duration of stay usually quoted for general hospitals. This is partly because several patients were admitted to hospital more than once during their period of absence, and the mean is based on the total time spent in hospital by each patient, and partly because some were admitted to sanatoria and mental hospitals, in which mean duration of stay is much longer than in general hospitals.

(*i*) *Interval between leaving work and entering hospital.*—The mean interval between leaving work and entering hospital (8 days) may seem unduly long. The mean is misleading; more than half (243) of the 427 hospital patients were admitted within 48 hours of leaving work. Of the 92 patients who were at home a week or more before admission to hospital, 23 were admitted as medical or surgical emergencies arising in the course of a domiciliary

illness and there is therefore no reason to believe that the interval could have been reduced. The remaining 69 patients had been waiting at home on the average 35 days for admission, 39 of them for surgical treatment, and 30 for medical investigation or treatment. While some of this delay may be attributable to the failure of general practitioners to refer patients quickly to hospital, it seems certain that it is due mainly to the difficulty of obtaining early admission for illnesses other than emergencies. Expansion of the rehabilitation services cannot of course be expected to have any effect on this interval, but in determining priority of admission hospitals might well consider not only the medical needs of the patient, but also whether it will be necessary for him to leave work while awaiting admission.

(*ii*) *Interval between hospital discharge and return to work.*—As noted above, the mean interval between hospital discharge and return to work was 54 days, and Table VII gives the distribution of patients according to the length of this interval. Only about one-fifth were at work within 4 weeks; two-fifths were away for 8 weeks or more.

TABLE VII

INTERVAL BETWEEN DISCHARGE FROM HOSPITAL AND RETURN TO WORK

Patients Admitted to Hospital	Interval (wks)				
	0–	4–	8–	12 and over	Total
Number	93	169	102	63	427
Percentage ..	21·8	39·6	23·9	14·8	100

To decide whether the period of post-hospital absence could be reduced by improved rehabilitation services, we must relate the interval to diagnosis and treatment. Unfortunately this can be done on reasonable numbers only in the case of patients submitted to certain operations. Table VIII shows that there are substantial differences in the interval,

(*a*) according to the nature of the operation (as would be expected),

(*b*) between persons of the same sex submitted to the same operation.

In an attempt to find an explanation for very prolonged absences we examined the records of the 26 patients entered in Table VIII who were away from work 10 weeks or more after leaving hospital. At least seventeen of them had medical reasons for absence of a kind unlikely to be much affected by physical treatment*. For the remaining nine patients information was incomplete, but in the opinion of the medical officers none would have benefited from physical treatment.

TABLE VIII

DISTRIBUTION OF PATIENTS ACCORDING TO INTERVAL BETWEEN DISCHARGE FROM HOSPITAL AND RETURN TO WORK

Operation	Interval (wks)								
	2–	4–	6–	8–	10–	12–	14–	16 and over	Total
Herniotomy (males) ..	2	15	8	5	5	–	–	1	36
Partial gastrectomy (males)	–	4	2	3	1	1	–	1	12
Hysterectomy (females) ..	–	1	–	2	7	–	2	3	15
Acute appendicectomy (both sexes)	12	10	6	4	1	2	–	1	36
Haemorrhoidectomy (both sexes) ..	3	3	1	1	–	–	–	1	9

The cases examined do not therefore suggest that improved physical treatment would have contributed materially to reduction of the duration of post-hospital absence. This is consistent with the assessment made by the medical officers, who considered that only 2·8 per cent. (12) of hospital patients might have benefited during convalescence from physical treatment which they had not received (Table III).

(*b*) PATIENTS NOT ADMITTED TO HOSPITAL.—We are unable to come to any firm conclusion about the probable effect of improved physical treatment on the duration of absence in patients not admitted to hospital. It will be recalled that it is for this group that existing services appear to be most deficient (Table III). Of the 1,149 patients, 103 might have benefited from treatment, but there are two reasons, neither of them conclusive, for doubting whether this treatment would have appreciably shortened the time lost from work:

(*a*) of the 184 patients absent 12 weeks or more, the proportion requiring, but not receiving, treatment (8 per cent.) was about the same as the proportion of the 965 absent less than 12 weeks (9 per cent.);

(*b*) among the patients absent 12 weeks or more who were considered to require physical treatment, there was no substantial difference between the treated and the untreated (125 and 124 days respectively) in mean duration of absence.

DISCUSSION

It has been shown that the incidence of prolonged absence from work because of sickness or accident is

* For example a man past retiring age, absent 143 days after herniotomy, and a woman aged 51, absent 142 days after hysterectomy, both developed post-operative broncho-pneumonia; another woman who lost 116 days had a coronary thrombosis during convalescence after appendicectomy; the patient with the longest period of post-hospital absence (215 days) developed septicaemia after haemorrhoidectomy.

high both among patients admitted and among those not admitted to hospital. According to the assessment of the works' medical officers, 7 per cent. of those absent more than a month would have benefited from physical treatment which they had not received, the need being most conspicuous among patients not admitted to hospital.

Although additional rehabilitation services would undoubtedly contribute to the welfare of some patients, the data do not suggest that they would have much effect upon the mean duration of absence. So far as we can judge this is determined mainly by medical conditions unlikely to be much affected by physical treatment, and by the method of payment during absence. The importance of the financial incentive was recently emphasized by Buzzard and Shaw (1952), and our own data show that among patients not admitted to hospital the mean duration of absence was 9 days longer for patients paid by the firm (67 days) than for patients whose wages ceased upon leaving work (58 days); among patients admitted to hospital the difference between the two groups was insignificant.

These considerations suggest that the case for expansion of the rehabilitation services rests upon their contribution to the welfare of patients, rather than upon their effect on the duration of absence from work. Two suggestions may be made about their organization. In the first place, it would reduce the pressure on the staff of hospital out-patient departments if general practitioners could have direct access to these services without referring patients to a consultant. Secondly, the services should be provided at the place of work wherever possible, so that patients can return to work while continuing treatment.

Summary

(1) An investigation of the need for physical treatment during prolonged absence from work is based upon the experience of six large firms with a total of 30,486 employees. The medical officers of these firms interviewed on return to work all absentees who left work because of sickness or accident between October 1, 1950, and September 30, 1951, and who were absent for 28 or more consecutive days.

(2) Approximately one in twenty employees (in one firm one in ten) had been away for at least one month during the year, and 1·4 per cent. had been in hospital. Mean durations of absence for persons admitted and not admitted to hospital were 83 and 60 days respectively. For patients admitted to hospital mean durations of absence before admission, in hospital, and after discharge were 8, 21, and 54 days respectively.

(3) 8·7 per cent. of patients had received some form of physical therapy, and the medical officers considered that a further 7·3 per cent. needed treatment but had not received it. 14·5 per cent. had been admitted to a convalescent home, and it was thought that a further 17·8 per cent. might have benefited from admission.

(4) Although additional facilities for physical treatment would undoubtedly contribute to the welfare of patients, the data do not suggest that they would have much effect upon the mean duration of absence.

This survey was made possible by the generous co-operation of Messrs. Birmid Industries; Cadbury Bros.; Guest, Keen, and Nettlefolds; Imperial Chemical Industries; Rubery Owen and Co.; and Stewarts and Lloyds Ltd. We are greatly indebted to the medical officers of these firms: Drs R. Wright, R. L. Ferguson, W. L. Lloyd, N. G. Marr, J. A. Duncan, V. V. Brown, and A. K. Hill.

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